LEVOTHYROXINE THERAPY IN PATIENTS WITH HYPOTHYROIDISM

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LEVOTHYROXINE THERAPY IN PATIENTS WITH HYPOTHYROIDISM

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Table of Contents

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EDITORIAL
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Editorial: Levothyroxine Therapy in Patients With Hypothyroidism

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Keywords: levothyroxine, hypothyroidism, thyroid-stimulating hormone (TSH), tablet L-T4, soft gel capsule L-T4, liquid L-T4, malabsorption

Editorial on the Research Topic

Levothyroxine Therapy in Patients With Hypothyroidism

Hypothyroidism is a condition that is more frequent in women, particularly those older than 60 years of age. It is readily diagnosed by the measurement of blood levels of thyroid-stimulating hormone (TSH) and thyroxine (T4) (1). Common causes of hypothyroidism include (2–4): A) a low iodine intake in iodine deficient areas; B) autoimmune thyroiditis (the principal cause in iodine sufficient areas); C) total thyroidectomy; D) radioiodine therapy as for therapy of hyperthyroidism; E) drugs (i.e., immune checkpoint inhibitors, and tyrosine kinase inhibitors) (5–7); F) other rare causes (8).

Levothyroxine (L-T4) is a synthetic hormone with a chemical structure similar to natural endogenous T4, that is prescribed at the dose of 1.5-1.7 μg/kg body weight/day as substitutive therapy for any of the conditions associated with hypothyroidism. The treatment will lower elevated levels of TSH into the normal range for virtually all hypothyroid patients, with normalization as well of circulating free triiodothyronine (FT3) and free T4 (FT4) levels (1, 9). Nevertheless and owing to various interfering issues, ~20-50% of patients do not have an optimal response to this therapy (10, 11), and require titration with higher dosage while monitoring TSH and thyroid hormones levels (12). Pseudomalabsorption of L-T4 caused by poor patience adherence to the prescribed dosage must be excluded, and having done so, then a decreased intestinal absorption of L-T4 associated with either intrinsic gastrointestinal diseases or pharmacological interference with absorption, remains the primary explanation for refractory hypothyroidism (11).

In the twelve papers that constitute this Research Topic, various innovative aspects related to therapy of hypothyroidism with L-T4 are reviewed and discussed and provide a stimulating overview of the present state of our knowledge.

The review by Fallahi et al. discusses novel L-T4 formulations such as the liquid preparation (that does not need the dissolution of the tablet preparation in the acid gastric environment) and the soft gel capsule (that dissolves quickly in the stomach), both of which having been developed to potentially bypass the problem of refractoriness reported with "usual formulations" of L-T4.

The use of the soft gel capsule of L-T4 has been studied in some clinical trials with promising results in subjects with gastric- or coffee-associated T4 malabsorption (13), as well as in hypothyroidism without demonstrable malabsorption.

Liquid L-T4 can avoid possible absorption interference related to coffee or food that has been reported with L-T4 tablets, and may overcome the problem of malabsorption observed in the

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presence of an elevated gastric pH as in atrophic gastritis (14), or with proton pump inhibitors treatment, or in subjects infected with Helicobacter pylori (HP) (15). Moreover, the liquid L-T4 preparation can bypass the malabsorption in subjects undergone to bariatric surgery (16), or with lactose intolerance (LI) (17). Ideally a liquid, rapidly absorbed preparation could maintain desirable TSH levels (in the reference range) in hypothyroid patients regardless of malabsorption, gastric disorders, or drug interference (18, 19), or in patients with intestinal parasites, gluten sensitivity, or celiac disease (CD).

The review by Virili et al. focuses on the state of our knowledge of the pathophysiologic pathways that determine the absorptive fate of the tablet versus alternative L-T4 formulations (softgel capsule and liquid solution) in patients with gastric disorders.

The review by Benvenga deals with the different medications which can interfere with L-T4, discussing also the costs associated with the frequent evaluation of TSH levels when L-T4 is administered contemporaneously with the interfering drug, and the metabolic and/or cardiovascular complications observed in undertreated hypothyroidism.

While the link between subclinical hypothyroidism and cardiovascular diseases has been suggested by many studies (20), the L-T4 treatment of subclinical hypothyroidism to decrease cardiovascular disease risk has not been proven to be necessarily advantageous. As reviewed in the paper by Sue and Leung, until now most of the international societal guidelines suggest that treatment decisions should be personalized according to the patient age, cardiovascular risk, degree of circulating TSH elevation, symptoms, and comorbidities. Moreover, caution should be taken in beginning L-T4 therapy for subclinical hypothyroidism in the elderly, as also reported in the paper by Effraimidis et al. The comorbidities that are present in older patients confound the correct diagnosis with that of non-thyroidal illness. It is controversial whether the treatment of such mild forms of hypothyroidism can ameliorate mortality, morbidity, and quality of life in elderly.

In their paper, Zijlstra et al. determine the effects of L-T4 therapy on cardiovascular outcomes in older adults with subclinical hypothyroidism. The reported findings indicated that L-T4 did not significantly change the risk of cardiovascular outcomes in older adults with subclinical hypothyroidism, regardless of a history of cardiovascular disease and age.

As described in the paper by Giuffrida et al., cystic fibrosis (CF) represents another cause of intestinal L-T4 malabsorption and the novel formulations of L-T4 may be effective in hypothyroid patients to overcome malabsorption. The data suggest that L-T4 in oral liquid formulation can overcome, at least in part, the reduced absorption of L-T4 in CF patients, leading to more tailored choices and a better management of hypothyroidism.

Patients who have undergone either lobectomy or total thyroidectomy represent another unique population with challenges to the attainment of an optimal L-T4 dose to restore euthyroidism (21, 22). The paper by Miccoli et al. discusses the multiple issues related to L-T4 treatment that apply to thyroidectomized patients. In spite of the attempts to devise a therapeutic scheme or reproduceable formula able to predict the exact dosage of L-T4 required after total thyroidectomy, it has not been possible to do so.

Of patients undergoing thyroid surgery, those with thyroid cancer (TC) represent a unique and heterogeneous population in regard to subsequent L-T4 dosage in that optimal dosage will likely depend on whether or not there is residual tumor post-operatively and hence the need for TSH-suppressive L-T4 therapy rather than replacement dosage. The study by Dou et al. intends to determine the proportion of patients among those with low-risk papillary TC (PTC) who do not need substitutive or replacement therapy based on the presence of risk factors for post-lobectomy hypothyroidism. Of note in this regard was their conclusion that patients with lower preoperative TSH levels undergoing lobectomy and without Hashimoto's thyroiditis, are more likely to have a normal thyroidal function in the first year after thyroidectomy.

Epidemiologic issues surrounding the incidence of hypothyroidism are examined in the paper by Kim et al. which offers an evaluation of both the incidence of hypothyroidism and a determination of the factors associated with hypothyroidism that lead to the need for thyroid hormone replacement. The Authors suggest that patients with an elevated risk of postoperative hypothyroidism should be made aware of their risk factors and should be monitored more intensively.

Prior to the availability of recombinant human TSH (Thyrogen) for the preparation of TC patients for radioiodine scanning and/or therapy and as still done in many medical centers, L-T4 therapy was withdrawn for 4-6 weeks in order to elevate endogenous TSH sufficiently to stimulate isotope uptake. Such withdrawal is of course a cause for hypothyroidism, albeit of limited duration. It has been noted that TC patients often display mood disorders after the withdrawal of L-T4, but it is still not known whether the disorders are related to the withdrawal of L-T4 per se or to the duration of the withdrawal or indeed some other possible mechanism. The paper by Wu et al. investigates the abnormal regional cerebral glucose metabolism (rCMRglu) in PTC patients without L-T4 for 4 weeks, in an attempt to explain the mechanism leading to mood disorders associated with transient hypothyroidism.

Recent large population studies have suggested that the high TSH levels in the range seen in subclinical or clinical hypothyroidism are associated with an increased mortality in patients treated with L-T4, independent of patient age (23, 24). These studies stimulate the need to examine this issue in future large prospective population studies in patients treated with L-T4.

Importantly, although modern approaches to L-T4 therapy has been in use for more than 60 years, cross-sectional studies have reported that ~45% of patients are either over- or under-treated. As extensively discussed in the paper by Antonelli et al., in the long term follow-up liquid L-T4 maintains normal TSH values more efficiently than L-T4 tablets, both in patients with no malabsorption, or in those with a malabsorptive state.

In conclusion, novel oral L-T4 preparations (soft gel capsule and liquid formulation) represent the most recent and welcome advances in levothyroxine therapy, and the content herein of this Research Topic provides an extensive update of the literature extant, and suggests potential directions for future research.

AUTHOR CONTRIBUTIONS

AA, LW and PM have equally contributed to the draft of the Editorial. All authors contributed to the article and approved the submitted version.

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Thyroid Hormone Supplementation Therapy for Differentiated Thyroid Cancer After Lobectomy: 5 Years of Follow-Up

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Background: Lobectomy with preservation of the contralateral lobe has already become the most preferred surgical method for patients with low-risk thyroid cancer. The incidence of and risk factors for the development of hypothyroidism after lobectomy for thyroid cancer remains unclear. The previous practice of levothyroxine supplementation post-thyroidectomy, to bring about thyroid stimulating hormone (TSH) suppression, had some serious side effects. This study aimed to evaluate the incidence of hypothyroidism and to identify the factors associated with hypothyroidism requiring thyroid hormone replacement.

Methods: We retrospectively reviewed the charts of 256 consecutive patients with differentiated thyroid cancer treated with lobectomy at the Gangnam Severance Hospital between April and December 2014 who were followed-up for more than 5 years. Patients were evaluated using a thyroid function test at the time of outpatient visit every 6 months for the 1st year, with an annual follow-up thereafter.

Results: After 5 years, 66.0% (169) of the patients needed levothyroxine supplementation to maintain euthyroid status. The incidence of hypothyroidism requiring levothyroxine supplementation increased until 3 years but showed no significant change in the 4 and 5th year. Recurrence showed no difference between the group with and without levothyroxine supplementation. The presence of thyroiditis and preoperative TSH levels were correlated with postoperative levothyroxine supplementation to maintain euthyroid status, in univariate and multivariate analyses.

Conclusion: High preoperative TSH levels and/or thyroiditis indicate a significantly increased likelihood of developing hypothyroidism requiring thyroid hormone supplementation after a thyroid lobectomy. Patients with an increased risk of postoperative hypothyroidism must be aware of their risk factors and should undergo more intensive follow-ups.

Keywords: thyroid stimulating hormone suppression, hypothyroidism, low-risk differentiated thyroid cancer, levothyroxine supplementation, thyroid lobectomy

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INTRODUCTION

With the improvement in early diagnosis, the proportion of patients with low-risk differentiated thyroid cancer (DTC) is also increasing. Lobectomy with preservation of the contralateral lobe has already become the most preferred surgical method for patients with low-risk thyroid cancer (1).

The incidence of and risk factors for the development of hypothyroidism after lobectomy remain unclear. Several studies have demonstrated an incidence of post-thyroidectomy hypothyroidism ranging from 9 to 43% depending on the duration of follow-up evaluation and the definition of hypothyroidism among patients who undergo lobectomy (2–4).

Thyroiditis, preoperative thyroid stimulating hormone (TSH) levels, and positivity for thyroid antibodies have been reported to be the most important risk factors for early and late postoperative hypothyroidism (2, 5, 6).

The American Thyroid Association guidelines recommend TSH levels to be in the mid to lower reference range (0.5–2 mU/L) for low-risk patients who have undergone lobectomy, with continued surveillance for recurrence (1). The purpose of levothyroxine therapy is not only to replace the endogenous thyroid hormone to treat hypothyroidism but also to prevent the relapse or progression of thyroid cancer; furthermore, it plays a central role in papillary thyroid carcinoma (PTC) management after thyroidectomy (5, 7). TSH suppression, resulting in serum TSH levels below the lower limit of the reference range, was proposed as a therapeutic intervention in thyroid cancer, on the assumption that subnormal serum levels of TSH would slow the growth and spread of thyroid cancer cells (8). While TSH suppression improves disease specific survival in high-risk patients, its benefits in low-risk patients is controversial (5, 7).

TSH suppression, brought about by the long-term administration of supraphysiological doses of levothyroxine, could cause some serious side effects including symptoms and signs of hyperthyroidism and impaired psychological, social, and physical quality of life (9, 10). Increased risks of osteoporosis and fractures, particularly in postmenopausal women, have been reported (11). Moreover, adverse effects on the heart including increased cardiovascular morbidity and mortality are known to be associated with TSH suppression (9, 10, 12).

Defining the risks of hypothyroidism is crucial for developing better preoperative counseling and management strategies and follow-up strategies for patients undergoing this lobectomy. Until now, not much is known about which patients should be carefully followed-up and how the interval of follow-up should be modified.

This study was designed to evaluate the incidence and timing of development of hypothyroidism after lobectomy and to analyze the relationship of post-thyroidectomy hypothyroidism with preoperative parameters and histopathological findings.

Abbreviations: DFS, Disease-free survival; DTC, Differentiated thyroid cancer; PTC, Papillary thyroid carcinoma; SD, Standard deviation; TSH, Thyroid stimulating hormone; CI, Confidence interval.

MATERIALS AND METHODS

Patients

Among the patients who visited the Thyroid Cancer Clinic at Gangnam Severance Hospital, Yonsei University, 256 consecutive patients who underwent lobectomy for low-risk PTC from April 2014 to December 2014 were enrolled. Patients who had an aggressive variant of papillary thyroid cancer or poorly differentiated thyroid cancer were not included. Patients with preoperative hypothyroidism, defined as patients with known diagnosed hypothyroidism, patients receiving preoperative thyroid hormone treatment for any reason, or patients with baseline TSH levels above the upper limit of the normal range at our institution (0.86–4.69 mcIU/mL) were excluded from the study.

The study was carried out in accordance with the principles laid out in the World Medical Association's Declaration of Helsinki, Good Clinical Practice, and associated Korean regulations. This study was approved by the Institutional Review Boards of Gangnam Severance Hospital. Since patients' identities remained undisclosed as data were obtained retrospectively and since informed consent is not mandatory for retrospective studies in Korea, the institutional review board waived the need for informed consent.

A lobectomy was defined as the resection of either the right or left thyroid lobe with preservation of the isthmus and the contralateral thyroid lobe.

All patients were followed-up postoperatively for at least 5 years from 2014 to 2019. Outpatient follow-up was carried out according to a basic routine protocol: (1) outpatient visits every 6 months for the 1st year, with an annual follow-up thereafter, (2) a thyroid function test at every visit, and (3) an annual sonography follow-up.

Definition of Hypothyroidism

Postoperative hypothyroidism was defined as a serum TSH level greater than the normal range at our institution (0.86–4.69 mcIU/mL). Thyroiditis was defined as either the presence

TABLE 1 | Baseline characteristics of the patients who underwent lobectomy.

		Total patients (n = 256)
Age (years, mean ± *SD*)		43.79 ±10.92
Male		52 (20.3%)
Female		204 (79.7%)
Preoperative TSH (mcIU/mL, mean ± *SD*)		1.79 ± 0.94
Tumor size (cm, mean ± *SD*)		0.72 ± 0.46
Thyroiditis	Yes	87 (34.0%)
	No	169 (66.0%)
N stage	N0	187 (73.0%)
	N1a	69 (27.0%)
Recurrence		3 (1.2%)
Mean f/u (days, mean ± *SD*)		1998.7 ± 92.5

TSH, thyroid stimulating hormone; SD, standard deviation; f/u, follow-up.

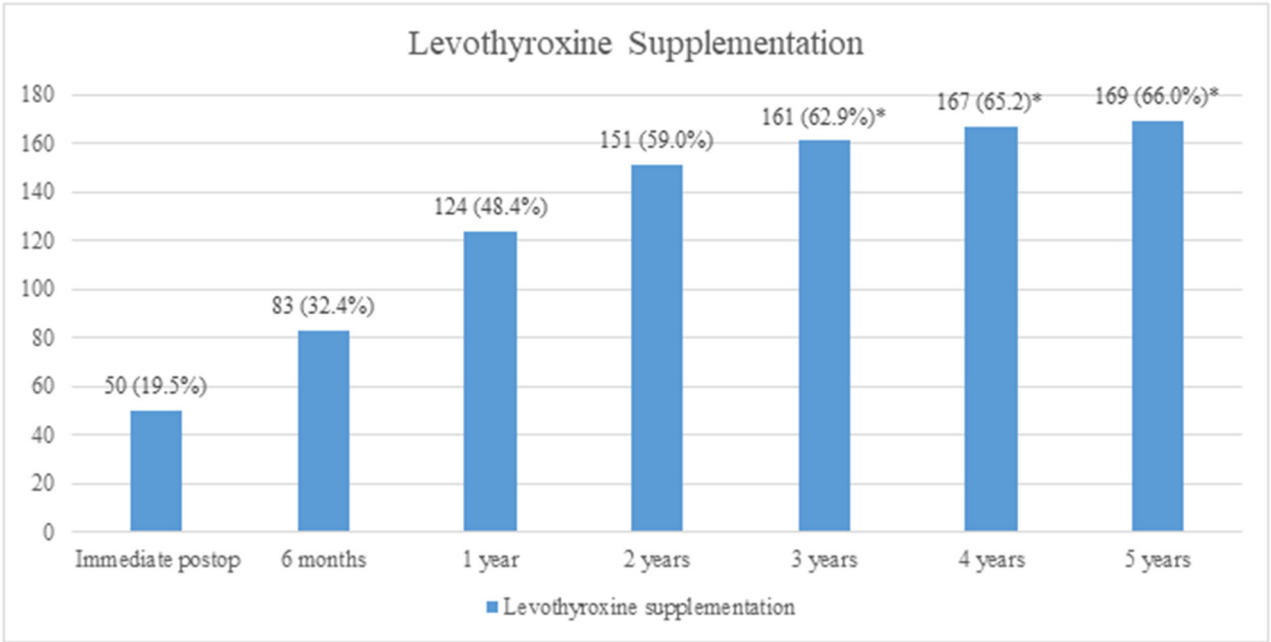

FIGURE 1 | Incidence of hypothyroidism and levothyroxine supplementation. A significant increase in incidence was observed until 3 years ($p < 0.001$), whereas after 3 years, there was no significant increase (*$p > 0.05$, analyzed by the McNemar's test).

of positive antibodies preoperatively (anti-thyroid peroxidase antibody or anti-thyroglobulin antibody) or if thyroiditis was diagnosed in a pathologic report.

Levothyroxine supplementation was administered to patients with TSH levels higher than the upper limit of the normal range at our institution.

Statistical Analysis

Descriptive statistics were used to describe the basic characteristics of the two groups. Continuous variables, expressed as mean ± standard deviation (*SD*), were compared using the Student's *t*-test. Pearson's chi-square test, Fisher's exact test, and McNemar's test were used for categorical variables, expressed as numbers and percentages. Univariate and multivariate analyses were performed by logistic regression analyses. All statistical analyses were performed using SPSS version 23.0 for Windows (SPSS Inc., Chicago, IL, USA). In all statistical analyses, a two-tailed $p < 0.005$ was considered statistically significant.

RESULTS

The clinicopathological characteristics of the patients included in the study are presented in **Table 1**. Of the 256 included patients, 169 (66.0%) needed levothyroxine supplementation during follow-up. In three patients (1.2%), recurrence was observed. Investigation of the recurrence site revealed that recurrence occurred in different sites in the three patients: contralateral lobe recurrence, early lung metastasis, and lateral lymph node metastasis.

TABLE 2 | Clinicopathological characteristics according to levothyroxine supplementation.

	No levothyroxine ($n = 87$)	Levothyroxine ($n = 169$)	*p*-value
Age (years, mean ± *SD*)	**43.31 ± 10.21**	**44.04 ± 11.28**	**0.032**
Sex (Female)	70 (80.5%)	134 (79.3%)	0.826
Preoperative TSH (mcIU/mL, mean ± *SD*)	**1.40 ± 0.59**	**1.99 ± 1.02**	**<0.001**
Tumor size (cm, mean ± *SD*)	0.77 ± 0.47	0.69 ± 0.44	0.452
Thyroiditis	**22 (25.3%)**	**65 (38.5%)**	**0.035**
Lymph node metastasis (N1a)	24 (27.6%)	45 (26.6%)	0.870
Recurrence	0 (0%)	3 (1.2%)	0.211

TSH, thyroid stimulating hormone; SD, standard deviation.
Bold values indicates statistically significant different ($p < 0.05$).

The patients were followed-up for a duration of 5 years. After lobectomy, 19.5% of patients were diagnosed with hypothyroidism immediately postoperatively, and levothyroxine supplementation was started. The incidence of hypothyroidism (with the need of levothyroxine supplementation) increased significantly during the first 3 years of follow-up ($p < 0.001$). After 3 years, there was no significant increase in the incidence of levothyroxine supplementation (**Figure 1**).

There were no significant differences in sex, tumor size, lymph node metastasis, and recurrence between the groups with and without levothyroxine supplementation. However, age, preoperative TSH levels, and the presence of thyroiditis were significantly different between the two groups (**Table 2**).

TABLE 3 | Univariate and multivariate analyses for clinical factors associated with levothyroxine supplementation.

	No levothyroxine ($n = 87$)	Levothyroxine ($n = 169$)	Univariate		Multivariate	
			OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age (years, mean ± *SD*)	43.31 ± 10.21	44.04 ± 11.28	1.006 (0.982–1.030)	0.614	1.002 (0.976–1.028)	0.889
Sex (Female)	70 (80.5%)	134 (79.3%)	1.076 (0.563–2.055)	0.826	1.138 (0.570–2.271)	0.714
Preoperative TSH (mcIU/mL, mean ± *SD*)	1.40 ± 0.59	1.99 ± 1.02	2.229 (1581–3.142)	<0.001	2.271 (1.598–3.227)	<0.001
Thyroiditis	22 (25.3%)	65 (38.5%)	1.847 (1.040–3.279)	0.036	2.021 (1.092–3.738)	0.025

TSH, thyroid stimulating hormone; SD, standard deviation; OR, odds ratio; CI, confidence interval.

In the univariate analysis, there was no correlation between age, sex, and the development of postoperative hypothyroidism, and the need of levothyroxine supplementation. Preoperative TSH levels and the presence of thyroiditis had a significant impact on the incidence of hypothyroidism and levothyroxine supplementation. This was also shown in the multivariate analysis (**Table 3**).

DISCUSSION

Our study showed that 66.0% of the patients who underwent lobectomy for PTC developed hypothyroidism and needed levothyroxine supplementation. An increase in the number of hypothyroid patients was observed during the first 3 years of follow-up, but after 3 years, there was no significant increase. The factors associated with hypothyroidism were preoperative TSH levels and thyroiditis. There was no difference in recurrence according to the use of levothyroxine supplementation. Although the patients in this study did not undergo TSH suppression and their TSH levels were maintained in the normal range considered in our hospital, there were only three recurrent cases.

In another study, the authors suggested that they may be able to predict the possibility of developing post-hemithyroidectomy hypothyroidism, especially in the presence of preoperative positivity for microsomal and thyroglobulin antibodies and high-grade lymphocytic infiltration of the resected gland (13). Since we defined "thyroiditis" as the presence of high preoperative levels of antibodies or lymphocytic infiltration in the pathologic report, our study showed the same results. Stoll et al. (14) reported that higher mean preoperative TSH levels, lower preoperative T4 levels, and the presence of Hashimoto's thyroiditis were significant risk factors for hypothyroidism. Specifically, patients with preoperative TSH levels >1.5 uIU/mL had a higher proportion of hypothyroidism. Furthermore, female sex could also be a potential risk factor for hypothyroidism after thyroid lobectomy, although this factor only showed a trend toward statistical significance. However, the above studies only included patients with benign pathology, while patients with malignancy were excluded.

The increase in the number of patients who needed levothyroxine supplementation was significant during the first 3 years, whereas there was no significant increase after 3 years. Therefore, we suggest that after lobectomy, patients should be regularly followed-up within short time intervals of 6–12 months for the first 3 years; after 3 years, the follow-up duration can be widened. One study reported that the majority of patients with hypothyroidism were detected during the first 6 months post-operation, and the authors suggested regular follow-ups for serum TSH testing for at least 12 months (13).

Studies have reported that about 14.3–42.6% of patients require thyroid hormone replacement after lobectomy. However, these studies included patients with benign disease and used higher TSH levels to define hypothyroidism (2, 13, 14).

In our study, there was no TSH suppression, and TSH levels were maintained in the normal range (0.86–4.69 mcIU/mL). However, there was no difference in recurrence depending on the incidence of hypothyroidism, and only three patients showed recurrences in this population during the 5 years of follow-up, suggesting that for low-risk DTC patients, there is no need for TSH suppression, and it is sufficient to maintain their TSH levels within the normal range. The findings of the study by Lee et al. support our findings in that considering the excellent prognosis of low-risk DTC and limitations of the effects of TSH suppression therapy, TSH suppression treatment is not necessary for patients who undergo lobectomy for low-risk DTC (15). Another study reported that serum TSH levels did not affect short-term recurrence in patients with low-risk DTC after thyroid lobectomy. During a 5-years follow-up, 1.4% of patients experienced recurrence. The mean TSH values did not affect recurrence-free survival. However, the mean TSH levels of patients in their study were within the recommended low-normal range (0.5–1.9 mIU/L) (16). Furthermore, a randomized controlled trial with low-risk PTC patients showed that disease-free survival (DFS) in patients without TSH suppression was not inferior by more than 10% to the DFS in patients with TSH suppression. The authors suggested that thyroid-conserving surgery without TSH suppression should be considered for patients with low-risk PTC to avoid the potential adverse effects of TSH suppression (17). However, the follow-up time in our study was only 5 years and required a more prolonged time of observation to follow-up for recurrence.

Research has been conducted not only on the effect of TSH suppression on cancer recurrence but also on its role in the prevention of nodular recurrence of benign disease. It has been reported that prophylactic levothyroxine

treatment after lobectomy significantly decreased the recurrence rate of nodular goiter in the contralateral thyroid lobe as well as the need for completion thyroidectomy, mostly among patients with iodine deficiency (18). Levothyroxine therapy may prevent the recurrence of nodular disease; furthermore, levothyroxine therapy at a substitutive dosage may be sufficient compared to TSH suppression (19).

In conclusion, interpretation of these results and related literature has several practical implications in clinical settings. High preoperative TSH levels and/or thyroiditis should alert the clinician to a significantly increased likelihood of hypothyroidism development and the requirement of thyroid hormone supplementation after thyroid lobectomy. Patients with an increased risk of postoperative hypothyroidism must be aware of their risk factors and should undergo more intensive follow-ups. However, two-thirds of patients who undergo lobectomy need levothyroxine supplementation; thus, from a practical standpoint, all patients who undergo lobectomy should be counseled regarding the potential need for lifelong thyroid hormone therapy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study was carried out in accordance with the principles laid out in the World Medical Association's Declaration of Helsinki, Good Clinical Practice, and associated Korean regulations. This study was approved by the Institutional Review Board of Gangnam Severance Hospital. As data were obtained retrospectively, patients identities remained, and informed consent is not mandatory for retrospective studies in Korea, the institutional review board waived the need for informed consent.

AUTHOR CONTRIBUTIONS

SK, S-MK, HC, H-SC, and CP contributed to the conception and design of the study. SK, HK, and YL organized the database. SK performed the statistical analyses, wrote the first draft of the manuscript, and wrote sections of the manuscript. All authors contributed to manuscript revision and read and approved the submitted version. All authors contributed to the article and approved the submitted version.

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Levothyroxine for the Treatment of Subclinical Hypothyroidism and Cardiovascular Disease

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Subclinical hypothyroidism is a biochemical condition defined by elevated serum thyroid-stimulating hormone levels in the setting of normal levels of the peripheral thyroid hormones, thyroxine and triiodothyronine. Thyroid hormones act on the heart through various mechanisms and subclinical hypothyroidism has been associated with risk factors for cardiovascular disease, such as hypertension and dyslipidemia. In addition, evidence from multiple studies supports an association between subclinical hypothyroidism and cardiovascular disease. However, the use of levothyroxine in subclinical hypothyroidism to reduce cardiovascular disease risk is not clearly beneficial. Treatment with levothyroxine may only provide benefit in certain subgroups, such as patients who are younger or at higher risk of cardiovascular disease. At present, most of the international societal guidelines advise that treatment decisions should be individualized based on patient age, degree of serum thyroid-stimulating hormone (TSH) elevation, symptoms, cardiovascular disease (CVD) risk, and other co-morbidities. Further study in this area is recommended.

Keywords: subclinical hypothyroidism, cardiovascular disease, levothyroxine, thyroid disease, thyroid treatment

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INTRODUCTION

Subclinical hypothyroidism (SCH) is a biochemical condition defined by elevated serum thyroid-stimulating hormone (TSH or thyrotropin) levels in the setting of normal levels of the peripheral thyroid hormones, thyroxine and triiodothyronine (1). Mild grade 1 SCH (upper limit of TSH 9.9 mIU/L) can be differentiated from more severe grade 2 SCH (TSH ≥10 mIU/L), with approximately 80–90% of SCH patients falling in the grade 1 category (1–3). Most commonly, SCH is caused by autoimmune thyroiditis but can be due also to other causes. Laboratory data in the recovery phase of thyroiditis, in the course of medication, and in the elderly are similar to SCH (1, 2) and may complicate the decision to treat with levothyroxine.

Symptoms of SCH may include fatigue, cold intolerance, weight gain, and constipation, as well as reduced mood, quality of life, cognitive function, and memory (1). The clinical symptoms are usually milder in individuals with SCH than those with overt hypothyroidism. They can be absent in

individuals with grade 1 SCH and are expected to increase in frequency and severity with increasing serum TSH concentrations (1, 2). Although it may vary by age, sex, race/ethnicity, and geography, the reported prevalence of SCH ranges from 0.4–16.9% in one review (4) to as high as 19.7% (5) and 20% (6) in other series. The prevalence of SCH increases with age and is highest among women, elderly, and those living in iodine-deficient regions (1–3, 7, 8).

The risk of progression from SCH to overt hypothyroidism is 3.3–11.4% per year (9, 10). Higher rates of progression are seen in those with grade 2 SCH (compared to grade 1 SCH), positive serum thyroid peroxidase (TPO) antibody titers, female sex, high baseline serum TSH levels, and baseline free T4 (FT4) levels at the lower end of the reference interval (1, 2, 9–13). In a Japanese population of elderly atomic bomb survivors, those with SCH had more than 4.5 times increased risk of progression to overt hypothyroidism, compared with controls, with a baseline TSH greater than 8 mIU/L predictive of progression; however, TSH levels also normalized in 53.5% of patients over the study period (14).

PATHOPHYSIOLOGY OF CARDIOVASCULAR DISEASE (CVD) RELATED TO SCH

Thyroid hormones act on the heart through various mechanisms. On a cellular level, thyroid hormone regulates cardiac gene expression through its actions on cardiomyocytes and in the activity of ion channels (sodium, calcium, potassium) in the cardiomyocyte cell membrane; thyroid hormones also influence the cardiovascular system through their effects on peripheral circulation (15, 16). Thyroid hormone receptors can be found in the myocardium and in vascular endothelium, which allows for regulation of these tissue processes, including endothelial nitric oxide production and vascular tone (16).

SCH has been associated with various risk factors for CVD, such as hypertension and dyslipidemia. Increased blood pressure in SCH may be a result of reduced thyroid hormone-mediated endothelial-dependent vasodilation (16). Specific to dyslipidemia, decreased activity of both lipoprotein lipase activity in adipose tissue and hepatic lipase activity in the liver are thought to contribute to increased serum triglyceride levels (17). A reduced number of low-density lipoprotein (LDL) receptors and decreased cholesterol breakdown may also explain the dyslipidemia seen in SCH (16). In addition to increasing metabolic risk factors, SCH may negatively impact cardiac function itself, with studies demonstrating a possible role of liothyronine (T3) in mitochondrial function and repair/damage (18) and the improvement of cardiac output and reduction of peripheral vascular resistance upon T3 administration (19). Other studies have found that SCH is also associated with decreased ejection fraction, decreased arterial compliance, and increased risk of heart failure, possibly through increased renin-angiotensin-aldosterone axis activation, increased vasoconstriction, increased sympathetic activity, and reduced renal blood flow and glomerular filtration rates (16, 17).

ASSOCIATIONS BETWEEN SCH AND CVD

Numerous studies have explored the possible associations between SCH and CVD, a leading cause of death worldwide that accounts for one third of all deaths (20). The major studies on this topic will be reviewed here. Of note, the relationships between SCH, serum TSH levels, and specific risk factors for CVD, such as blood pressure (6, 21, 22), glucose levels (6), and cholesterol levels (6, 23–27), have also been examined but will not be reviewed in detail.

Evidence from multiple studies supports an association between SCH and CVD. Early studies suggested an association between SCH and CVD, but sample sizes were small (28, 29). In an observational study of postmenopausal women in the Netherlands, those with SCH had an increased prevalence of myocardial infarction [odds ratio (OR) 2.3, 95% confidence interval (CI) 1.3–4.0]; this risk was even higher among those with positive serum TPO antibodies (OR 3.5, 95% CI 1.7–7.4) (30). Women with SCH, either with or without the presence of TPO antibodies, also had a higher risk of aortic atherosclerosis (30). The calculated population attributable risk of SCH to myocardial infarction in the study was 14%, similar to those calculated for hypertension, diabetes, smoking, and hypercholesterolemia (14–18%) (30). In another study of Medicare patients (age 65 years or older) with SCH, those with a TSH greater than 10 mIU/L had a significantly higher prevalence of coronary heart disease compared with those whose TSH was less than or equal to 4.6 (52.6% versus 25.0%; $p = 0.007$) (31). In a Danish primary care population of 1,212 patients age 20–69 years without previous thyroid disease, biochemical SCH was associated with increased CVD, but only among men younger than 50 years old (OR 3.3, 95% CI 1.6–6.8) (5).

An Australian study of 2,108 patients (mean age, 50 years), was the first longitudinal study to demonstrate a positive relationship between SCH and cardiovascular events [hazard ratio (HR) 1.7, 95% CI 1.2–2.4, $p < 0.01$], which persisted after adjustment for cardiovascular risk factors and pre-existing thyroid disease or goiter (HR 1.8, 95% CI 1.7–2.7, $p < 0.01$), suggesting that the association may be driven by mechanisms other than established cardiovascular risk factors (32). Other cohort studies have shown similar associations, such as a study among adults in Taiwan without baseline thyroid disease [relative risk (RR) of cardiovascular death 1.68, 95% CI 1.02–2.76, $p < 0.05$] (33) and a re-analysis of the Whickham Survey cohort (HR of ischemic heart disease 1.76, 95% CI 1.15–2.71, $p = 0.01$) (21), although the original analysis had shown no association between SCH and CVD (9) and the association was not significant when levothyroxine treatment was removed from the model (21).

HUNT, a large prospective population-based cohort study of 25,313 individuals in Norway, found that TSH levels within the reference range were significantly positively associated with risk of incident cardiovascular death in the total population (P for trend 0.01) and among women (HR 1.41, 95% CI 1.02–1.96 for TSH 1.5–2.4 mIU/L; HR 1.69, 95% CI 1.14–2.52 for TSH 2.5–3.5 mIU/L; compared with TSH 0.50–1.4 mIU/L; P for trend 0.005)

over a median follow-up of 8.3 years (34). The positive association among women was attenuated by adjustment for blood pressure, serum cholesterol levels, body mass index, serum creatinine level, and use of antihypertensive medications, but remained statistically significant (HR 1.30, 95% CI 1.06–1.60). There was no association between TSH values above the reference range (in participants with SCH) and cardiovascular death. An update performed at 12 years of follow-up among the HUNT study participants again demonstrated an association between baseline TSH in the higher end of the reference range and incident cardiovascular mortality among women (HR 1.41, 95% CI 1.06–1.87 for TSH 1.5–2.4 mIU/L; HR 1.45, 95% CI 1.01–2.08 for TSH 2.5–3.5 mIU/L; compared with TSH 0.50–1.4 mIU/L; P for trend 0.005) and between SCH and cardiovascular mortality among women (HR 1.76, 95% CI 1.21–2.56); however, this increased risk did not translate into higher risk of hospitalization for myocardial infarction (35).

Among those with higher baseline CVD risks, the presence of SCH may further increase the risk of cardiovascular outcomes. Cardiac patients with SCH who were admitted to an Italian hospital had 2.4 times higher risk of cardiac death (95% CI 1.36–4.21, p = 0.02), compared with patients who were euthyroid (36). In Korean patients with high cardiovascular risk, defined by an Atherosclerotic Cardiovascular Disease (ASCVD) risk score >7.5% or known CVD, and TSH values in the highest quartile (>6.57), the risk of cardiovascular events was 2.42 times higher (95% CI 1.35–4.33), compared with euthyroid patients (37). Data from a study of patients at high risk for ASCVD at the Cleveland Clinic Preventive Cardiology Clinic revealed higher all-cause mortality among untreated patients, those younger than age 65 years, and in those with serum TSH levels between 6.1–10 mIU/L or greater than 10 mIU/L (38).

In a large individual-participant pooled analysis of prospective cohort studies (n = 55,287) by the Thyroid Studies Collaboration, SCH and coronary heart disease were positively associated in adults with TSH 10–19.9 mIU/L (HR 1.89, 95% CI 1.28–2.80), compared with those with normal TSH levels, with the risk further increasing the higher the serum TSH level was (P for trend <0.001) (39). Another large pooled analysis of over 31,900 participants, also done by the Thyroid Studies Collaboration, found that the increased risk of coronary heart disease events in those with SCH did not vary by serum TPO antibody status (P for interaction = 0.65) (40). SCH has also been associated with all-cause mortality, mediated by CVD, in a study that used data from the National Health and Nutrition Examination Survey in the United States (41).

In contrast, multiple studies have found insufficient evidence to support an association between SCH and CVD. The Cardiovascular Health Study was a large prospective cohort study that enrolled 3,233 elderly patients, including 496 (15%) with SCH (42). There was no difference in prevalent coronary heart disease cases at baseline between patients with SCH (19.8%) and those who were euthyroid (18.5%). There was also no difference in incident coronary heart disease cases (HR 1.07, 95% CI 0.90–1.28), compared with euthyroid patients, or in death from cardiovascular causes (HR 1.16, 95% CI 0.92–1.46). In a follow-up study with more participants, including 4,184 euthyroid and 679 with SCH, there was again no association between persistent SCH and incident coronary heart disease (HR 1.12, 95% CI 0.93–1.36) or cardiovascular death (HR 1.07, 95% CI 0.87–1.31) (43).

In a subset of the MrOS study (n = 1,587), a prospective study in the U.S. of elderly men to evaluate healthy aging and fracture risk, having SCH increased the risk of cardiovascular death, but the number of participants with SCH was small and the associations were not significant [TSH <10 mIU/L: relative hazard (RH) 1.28, 95% CI 0.77–2.14; TSH ≥10 mIU/L: RH 3.32, 95% CI 0.82–13.45] (44). In a nested case-cohort study of the Women's Health Initiative, there was no association between risk of myocardial infarction and SCH among postmenopausal U.S. women with varying degrees of SCH and serum TPO antibodies. Compared with euthyroid individuals, the HR for incident myocardial infarction was 0.90 (95% CI 0.47–1.74) among women with TSH of ≥7 mIU/L and positive serum TPO antibodies (45). SCH and cardiovascular events were also not associated in the Tehran Thyroid Study of 3,975 participants (mean age, 46.5 years; 189 participants with SCH) (HR 0.71, 95% CI 0.37–1.33) (46).

Several meta-analyses have summarized available data about SCH and the risk of CVD. Singh et al. examined several large cross-sectional and cohort studies published between 2000 through March 2006 (47). The meta-analysis found increased risk of prevalent coronary heart disease at baseline (RR 1.53, 95% CI 1.31–1.79; P <0.001; 5 studies) and incident coronary heart disease at follow up (RR 1.19, 95% CI 1.02–1.38; P <0.05; 3 studies) for those with SCH versus those without SCH. In addition, SCH was associated with higher risk of death from cardiovascular causes (RR 1.28, 95% CI 1.02–1.60; p <0.05; 3 studies) but not with all-cause mortality (RR 1.12, 95% CI 0.99–1.26; 3 studies) at follow-up. In a larger meta-analysis of published studies from 1977–2007 by Razvi et al. (48), the prevalence of ischemic heart disease was 23% higher in the SCH group compared with euthyroid subjects (95% CI 1.02–1.48; p = 0.03; 12 studies). Due to significant heterogeneity, however, subgroup analyses were performed; these analyses showed that the elevated risk of ischemic heart disease was only present in the subgroup of individuals younger than 65 years old (OR 1.57, 95% CI 1.19–2.06; p = 0.001; 7 studies) and not in the subgroup of individuals 65 years or older (OR 1.01, 95% CI 0.87–1.18; p = 0.01; 5 studies). Similarly, using data from available longitudinal cohort studies, SCH was associated with higher incidence of ischemic heart disease (OR 1.68, 95% 1.27–2.23; p <0.001; 3 studies) and cardiovascular mortality (OR 1.37, 95% CI 1.04–1.79; p = 0.02; 3 studies) but only among individuals younger than 65 years old.

A separate meta-analysis by Ochs et al. (49) suggested a mild positive association between SCH and coronary heart disease (RR 1.20, 95% CI 0.97–1.49; 10 studies), but this was again only statistically significant among younger individuals. Those with SCH who were younger than 65 years old had a 51% increase in risk of coronary heart disease (95% CI 1.09–2.09; 4 studies), compared with euthyroid individuals, versus an insignificantly increased risk for those with SCH who were 65 years or older

(RR 1.05, 95% CI 0.90–1.20; 6 studies). Similar estimates were seen in subgroup analyses of those under versus those over age 60 years old. There was also a suggested association between SCH and cardiovascular mortality (RR 1.18, 95% CI 0.98–1.42; 8 studies) in this meta-analysis.

The most recent and largest meta-analysis to date by Moon et al. included 555,530 participants from 35 studies, with 11 studies including individuals at high cardiovascular risk (as defined by CVD risk factors or any disease that could increase risk of CVD) (50). Compared with euthyroid participants, those with SCH had a 33% higher risk of CVD (95% CI 1.14–1.54). As expected, this risk was even higher among those at high CVD risk (RR 2.20, 95% CI 1.28–3.77). Because previous studies had suggested a difference in CVD risk by age (51), the authors performed additional subgroup analyses: the RR of SCH-associated CVD was 1.54 (95% CI 1.21–1.96) among those with a mean age less than 65 years and 1.07 (95% CI 0.97–1.18) among those with a mean age of 65 years or older. Similar findings were seen in the Moon et al. meta-analysis for all-cause mortality, with higher risk in those with high CVD risk and additional analyses observing an association only among the younger subgroup.

USE OF LEVOTHYROXINE IN SCH TO REDUCE CVD RISKS

There are limited data regarding the use of levothyroxine for improving CVD outcomes in individuals with SCH. These studies are summarized in **Table 1**. The Whickham Survey in Great Britain, which had found increased risk of ischemic heart disease in those with SCH, was the first study to suggest that treatment with levothyroxine may be beneficial in SCH. While there was no difference in ischemic heart disease events or ischemic heart disease-related mortality, comparing those treated (n = 20) versus not treated (n = 71) among study participants with SCH, there was a significant difference in all-cause mortality, with an 78% lower rate of death among those treated with levothyroxine (p = 0.02) (21). In another much larger retrospective cohort analysis using data from the United Kingdom General Practitioner Research Database (52), treatment of SCH with levothyroxine was associated with a significant reduction in fatal and nonfatal ischemic heart disease events, death due to circulatory diseases (ischemic heart disease, cerebrovascular disease, peripheral vascular disease), and all-cause mortality. However, these associations were seen only in younger subjects (age 40–70 years, n = 3,093) and not in older subjects (age greater than 70 years old, n = 1,642). The multivariate adjusted HRs for ischemic heart disease events, death due to circulatory diseases, and all-cause mortality were 0.61 (95% CI 0.39–0.95), 0.54 (95% CI 0.37–0.92), and 0.36 (95% CI 0.19–0.66), respectively. The significant association between treatment with levothyroxine and decreased ischemic heart disease events was again seen only in younger individuals when additional analyses were performed: 1) in a restricted dataset of only those with persistent SCH during the follow up-period in the untreated group, after exclusion of those who started levothyroxine treatment after SCH had already progressed to overt hypothyroidism; and 2) stratification of

TABLE 1 | Summary table of the use of levothyroxine in SCH to reduce CVD risks.

Authors	Year of Publication	Sample Size	Study Design	Population	Results
Razvi et al. (21)	2010	91	Cohort study	Middle-aged community-dwelling adults with SCH enrolled in the Whickham Study, a population-based cross-sectional study in northern England with 20 years of follow up.	Reduced all-cause mortality in those treated with levothyroxine: HR 0.22, 95% CI 0.06–0.81 (p = 0.02).
Razvi et al. (52)	2012	4,735	Cohort study	3,093 individuals age 40–70 years and 1,642 individuals age 71–107 years old with SCH from the United Kingdom General Practitioner Research Database. The median levothyroxine dose was 75 mcg daily.	In younger individuals (age 40–70 years) who received treatment with levothyroxine, there were fewer ischemic heart disease events (HR 0.61, 95% CI 0.39–0.95), deaths due to circulatory diseases (HR 0.54, 95% CI 0.37–0.92), and deaths due to any cause (HR 0.36, 95% CI 0.19–0.66).
Andersen MN et al. (53)	2015	12,212	Cohort study	Primary care adult patients 18 years or older in Copenhagen, Denmark diagnosed with SCH between 2000 and 2009	No association between treatment with levothyroxine and myocardial infarction, CVD death, or all-cause mortality. Benefit of levothyroxine treatment for all-cause mortality in patients less than 65 years old (incidence rate ratio 0.63, 95% CI 0.40–0.99).
Anderson MN et al. (54)	2016	1,192	Cohort study	Adult clinic patients 18 years or older in Denmark with existing heart disease diagnosed with SCH from 1997 to 2011.	No association between treatment with levothyroxine and major adverse cardiac events, all-cause mortality, MACE, or hospital admissions.
Stott et al. (55)	2017	737	Randomized controlled trial	Adults 65 years or older from Scotland, Ireland, the Netherlands, and Switzerland with untreated SCH randomized to a median daily levothyroxine dose of 50 mcg or placebo.	No significant differences in fatal or nonfatal cardiovascular events (HR 0.89, 95% CI 0.47–1.69), new-onset atrial fibrillation (HR 0.80, 95% CI 0.35–1.80), or all-cause mortality (HR 1.91, 95% 0.65–5.60) between the levothyroxine and placebo groups.
Blum et al. (56)	2018	158	Randomized controlled trial	Subset of participants from the Stott et al. study: Adults 65 years or older from Scotland, Ireland, the Netherlands, and Switzerland with untreated SCH randomized to a median daily levothyroxine dose of 50 mcg or placebo.	No significant differences in mean carotid intima media thickness (p = 0.30), maximum carotid intima media thickness (p = 0.35), or maximum plaque thickness (p = 0.86) between the levothyroxine and placebo groups.

SCH, subclinical hypothyroidism; CVD, cardiovascular disease; HR, hazard ratio; CI, confidence interval; MACE, major adverse cardiovascular events.

participants by serum TSH <6.6 mIU/L and TSH ≥6.6 mIU/L. In sensitivity analyses stratifying the study population by age per decade, the greatest and only statistically significant reduction in fatal and nonfatal ischemic heart disease events was seen in the 61-70 year old age group (HR 0.41, 95% CI 0.17–0.97). To date, there has been no large, randomized, placebo-controlled trial demonstrating a benefit of treatment with levothyroxine in SCH on CVD risk.

In contrast, data from some studies suggest that levothyroxine plays no significant role in improving CVD outcomes in individuals with SCH. The Thyroid Hormone Replacement for Untreated Older Adults with Subclinical Hypothyroidism – A Randomized Placebo Controlled Trial (TRUST) included 737 adults aged 65 years old or older, who were randomized to a daily levothyroxine dose of 25 or 50 mcg (then titrated by serum TSH level; median daily dose 50 mcg) or placebo (55). There were no differences in the primary outcomes of hypothyroid symptoms or tiredness on a thyroid-specific quality of life questionnaire at 1 year. Although the study was not powered to detect a difference in CVD incidence or mortality, analysis of adverse events showed no significant differences in fatal or nonfatal cardiovascular events (HR 0.89, 95% CI 0.47–1.69), new-onset atrial fibrillation (HR 0.80, 95% CI 0.35–1.80), or all-cause mortality (HR 1.91, 95% 0.65–5.60) in those treated with levothyroxine, compared with those in the placebo group. Overall event rates were so low for death from CVD and heart failure that HRs were not able to be calculated. In a smaller randomized, double-blind, placebo-controlled trial nested within the TRUST study (56), 158 participants were randomized to levothyroxine (titrated to normalization of serum TSH) or placebo; there was no difference in carotid intima media thickness or carotid atherosclerosis, both predictors of CVD, with levothyroxine treatment. Taken together, these data suggest that treatment with levothyroxine may not improve CVD outcomes in SCH, but also does not seem to cause significant risk.

A large cohort analysis of a primary care population of Danish patients with SCH (n = 12,212) evaluated the effect of treatment with levothyroxine over a median follow up of 5 years (53). Treatment with levothyroxine was not associated with incidence of myocardial infarction, CVD death, or all-cause mortality in this population; sub-group analyses by younger/older individuals and grade 1/grade 2 SCH also did not demonstrate any significant differences with levothyroxine treatment, except in patients less than 65 years old with respect to all-cause mortality (incidence rate ratio 0.63, 95% CI 0.40–0.99). In a similar but smaller population of Danish patients with existing heart disease and SCH (n = 1,192), there was also no association between levothyroxine treatment and major adverse cardiac events, all-cause mortality, or hospital admissions (54).

Multiple studies have suggested improvement in cholesterol parameters, blood pressure, and various markers of cardiac and vascular structure/function with levothyroxine treatment in SCH (25, 57–61), but generally these studies were small, the results need to be replicated, and any improvement in CVD risk factors with levothyroxine treatment may not ultimately translate into a reduction in CVD risk. A recent double-blind, randomized controlled trial that enrolled patients with acute myocardial infarction and SCH in hospitals in the United Kingdom found no difference in the primary outcome of left ventricular ejection fraction at 52 weeks, comparing the 46 participants in the treatment group (levothyroxine 25 mcg daily titrated to serum TSH levels between 0.4–2.5) with the 49 participants in the placebo group (62). An older small study of 40 women with mild SCH randomized participants to 50 mcg of levothyroxine daily or placebo: after 6 months, there was no significant difference in cholesterol, triglycerides, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, body mass index, or other parameters studied (63).

CURRENT GUIDELINES FOR THE TREATMENT OF SCH

A summary of guidelines on this topic from the various international organizations is provided in **Table 2**. The 2012

TABLE 2 | Summary of current guidelines for the treatment of SCH.

Society/Expert Panel	Year of Publication	Recommendations
American Thyroid Association (51)	2012	Primary hypothyroidism should be treated when the serum TSH is above 10 mIU/L and considered in those with increased CVD risk when the serum TSH is 4.5–10 mIU/L. The initial levothyroxine dose is typically lower in SCH than that required in overt hypothyroidism.
European Thyroid Association (64)	2013	Levothyroxine should be initiated in younger patients (age less than 65 years) who have serum TSH levels greater than 10 mIU/L and in younger patients with SCH who have symptoms consistent with hypothyroidism, even if the TSH is less than 10 mIU/L.
Latin American Thyroid Society (65)	2013	The decision to treat SCH should be based on the risk of progression to overt hypothyroidism. Levothyroxine should be initiated if the serum TSH is persistently greater than 10 mIU/L and considered if the serum TSH is 4.5–10 mIU/L in those younger than age 65 years with increased CVD risk.
American Thyroid Association (66)	2014	In those with SCH and known CVD, levothyroxine should be initiated at a low dose, increasing slowly as needed, and observed closely for the development of cardiac symptoms.
An international expert panel (findings published in the British Medical Journal) (67)	2019	Levothyroxine is generally recommended against for those with SCH, with the exception of women who are pregnant or trying to conceive or those with a serum TSH greater than 20 mIU/L. The recommendation may not apply to those with severe symptoms or those younger than 30 years old.

SCH, subclinical hypothyroidism; TSH, thyroid-stimulating hormone; CVD, cardiovascular disease.

American Thyroid Association guidelines for hypothyroidism in adults (51) recommend starting thyroid hormone treatment for primary hypothyroidism when the serum TSH is above 10 mIU/L and considering treatment in those with increased CVD risk when the serum TSH is 4.5–10 mIU/L. While there are limited outcome data on treating patients with TSH 2.5–4.5 mIU/L, the guidelines refer to studies demonstrating improved markers of atherosclerosis risk (lipids, endothelial function, and intima media thickness) in the consideration for treatment of SCH with serum TSH values in this range. The guidelines note that in SCH, the initial levothyroxine dose is typically lower than that required in overt hypothyroidism and suggest a daily dose of 25–75 mcg, depending on the degree of TSH elevation and to be adjusted based on symptoms and serum thyroid function test monitoring. For those with known CVD, the 2014 American Thyroid Association guidelines for the treatment of hypothyroidism recommend initiating levothyroxine at a low dose, increasing slowly as needed, and observing closely for the development of cardiac symptoms (66). A working group organized by the National Heart, Lung, and Blood Institute in the United States in 2017 identified three areas for future research in thyroid-related CVD: 1) basic biology linking thyroid dysfunction to CVD and thyroid hormone action in cardiovascular tissues; 2) identification of specific thyroid patients who might benefit from preventive interventions or treatments for CVD; and 3) clinical trials using thyroid pathways or thyroid treatments to influence CVD outcomes (68).

The 2013 European Thyroid Association guidelines on the management of SCH (64) recommend levothyroxine treatment in younger patients (age less than 65 years) who have serum TSH levels greater than 10 mIU/L and in younger patients with SCH who have symptoms consistent with hypothyroidism, even when the serum TSH is less than 10 mIU/L. These guidelines advise that in older individuals, age-specific reference ranges should be used to diagnose SCH. Observation without treatment should be the strategy of choice in patients greater than 80–85 years old with SCH and serum TSH less than or equal to 10 mIU/L. Levothyroxine is the thyroid hormone formulation of choice and the dose should be weight-based in patients without cardiac disease and start at a low amount (25 or 50 mcg daily) in those with cardiac disease and/or older age.

The 2013 Latin American Thyroid Society hypothyroidism management guidelines (65) recommend starting treatment in SCH based on how likely an individual is to progress to overt hypothyroidism. Therefore, the authors recommend starting thyroid hormone in individuals with a serum TSH persistently greater than 10 mIU/L and considering treatment initiation in those with a serum TSH 4.5–10 mIU/L who are younger than age 65 years with increased CVD risk (previous CVD, diabetes, dyslipidemia, hypertension, or metabolic syndrome), especially if the TSH is persistently greater than 7 mIU/L. The guidelines note that treatment could be considered for those with persistent mild elevations in TSH if serum TPO antibodies are positive and ultrasound findings are consistent with autoimmune thyroiditis. A lower grade recommendation is made for a short trial of levothyroxine in symptomatic middle-aged patients and continuation of this therapy if a clear benefit is seen. The guidelines recommend against treatment of elderly (older than 65 years) or very elderly (older than 80 years) patients with SCH and TSH levels less than 10 mIU/L.

Lastly and somewhat controversially, Bekkering et al. published a British clinical practice guideline in 2019 (67), which suggested a lack of benefit from thyroid hormone treatment in nearly all those with SCH, and specifically that asymptomatic SCH patients or those with non-specific symptoms should not be treated. The recommendation did not apply to women who are pregnant or trying to conceive or those with a serum TSH greater than 20 mIU/L and may not apply to those with severe symptoms or those younger than 30 years old, as evidence is limited in these subgroups. Commentary of the guideline argues that not enough evidence was provided to support the recommendation not to treat and that the decision to initiate treatment should be individualized based on degree of serum TSH elevation, symptoms, patient preference, and other factors (69, 70).

DISCUSSION

The role of levothyroxine for reducing the risk of CVD in individuals with SCH remains unclear. While SCH has been associated with both CVD and CVD risk factors, this is not consistent across all studies and the risk of CVD may be only significant elevated in younger individuals. Data from small studies showing improvements in CVD risk factors and markers of CVD risk may suggest some benefit of levothyroxine treatment in SCH; however, it is unclear if this risk reduction would ultimately confer a CVD or CVD mortality benefit. Furthermore, in larger observational and randomized, placebo-controlled studies, there is not yet convincing, consistent evidence that treatment with levothyroxine leads to reductions in CVD outcomes.

At the current time, most of the international societal guidelines advise that treatment decisions should be individualized based on patient age, degree of serum TSH elevation, symptoms, CVD risk, and other co-morbidities. Caution must be taken in initiating levothyroxine treatment for SCH in the elderly. Of note, there are different reference intervals that are applicable for specific sub-populations (the elderly, pregnant women), which may affect the decision to treat or not treat with levothyroxine. Further study in this area should include larger studies powered to detect differences in CVD incidence and CVD mortality, focusing on the identification of subgroups expected to benefit most from initiating levothyroxine treatment for SCH, while minimizing risks of treatment.

AUTHOR CONTRIBUTIONS

LS wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

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MINI REVIEW
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L-T4 Therapy in the Presence of Pharmacological Interferents

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Pharmacological interference on L-thyroxine (L-T4) therapy can be exerted at several levels, namely from the hypothalamus/pituitary through the intestine, where the absorption of exogenous L-T4 takes place. A number of medications interfere with L-T4 therapy, some of them also being the cause of hypothyroidism. The clinician should be aware that some medications simply affect thyroid function tests with no need of modifying the dose of L-T4 that the patient was taking prior to their prescription. Usually, the topic of pharmacological interference on L-T4 therapy addresses the patient with primary hypothyroidism, in whom periodic measurement of serum thyrotropin (TSH) is the biochemical target. However, this minireview also addresses the patient with central hypothyroidism, in whom the biochemical target is serum free thyroxine (FT4). This minireview also addresses two additional topics. One is the costs associated with frequent monitoring of the biochemical target when L-T4 is taken simultaneously with the interfering drug. The second topic is the issue of metabolic/cardiovascular complications associated with undertreated hypothyroidism.

Keywords: levothyroxine, hypothyroidism, pharmacological interferents, metabolic complications, cardiovascular complications

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INTRODUCTION

Prevalence of undiagnosed primary hypothyroidism (PH) in Europe is 4.76% (95% CI 2.98–6.79%), precisely 4.11% (3.05–5.31%) for subclinical hypothyroidism (SCH) and 0.65% (0.38–0.99%) for overt hypothyroidism (OH) (1), paralleling the American prevalence of 4.67, 4.34, and 0.3%, respectively (2). PH prevails in females, and in those aged ≥65 years (1). Central hypothyroidism (CH) was considered 1,000-fold rarer than PH, but it may be just 20-fold rarer (3). L-thyroxine (L-T4) monotherapy is the standard treatment for PH (4–6) and CH (4, 5, 7), and SCH patients candidate for replacement (4, 5, 8).

Thus, L-T4 is one top prescribed medication (9). However, ≈20% of patients with PH (10–13) and ≈20% (14) or 40% (15) of patients with CH are undertreated, co-administration of interfering medications (IM) being one major cause. Of 2,292 patients with PH (12), 42.7% had abnormal serum TSH (28.3% undertreated and 14.4% overtreated). Strikingly, only 52.1% of patients were told not to take L-T4 along with IM (12).

As mentioned below, there may be consequences on health from undertreated hypothyroidism (UTH).

THE PHARMACOLOGICAL INTERFERENCE ON L-T4 THERAPY

Such interference was covered by reviews (11, 16–19) chapters of books (10, 20–22), and guidelines (4, 5) with pertinent recommendations (4, 5) shown in **Table 1**.

Table 2 summarizes the mechanism(s) of interference and suggestions. The next paragraphs illustrate the author's experience. Of 210 L-T4-treated adult patients (tablet formulations) who were referred to SB in one year, 27 (13%) had UTH (11). In 8/27 (30%; 4% of 210), the explanation was pharmacological, all eight taking ≥1 drug that causes L-T4 malabsorption (proton-pump inhibitors [PPIs], calcium carbonate, ferrous sulfate) (11). A study with practitioners enrolled L-T4-treated PH (tablet formulations) that, for ≥2 years was not associated with drugs causing L-T4 malabsorption and that, for another ≥2 years, it was (23). Of 10,496 persons, 730 (7.0%) had L-T4-treated PH, of whom 391 (5.4%; 3.7% of 10,496) were taking those IM, with 114 enrolled (age 65.6 ± 12.7 years). PPIs were the leading IM (95/114 [83%]), either alone (n = 71 [62%]) or associated with other IM (n = 24 [21%]), followed by calcium salts (18/114 [16%]).

Another study evaluated changes in number of L-T4 prescriptions and dose of L-T4 before and during exposure to potential drug–drug interactions (DDIs) (24). In 5,426 L-T4 users aged ≥18 years (7.5% of persons under care), prescriptions and doses of L-T4 increased during exposure by 6 and 5%, respectively, suggesting that clinicians increase the number of L-T4 prescriptions to achieve TSH levels as low as those before DDIs (24).

A retrospective study evaluated TSH changes in 10,999 Scottish residents who were prescribed L-T4 before starting IM (25). Iron, calcium, PPI, and estrogens increased TSH significantly, with an increase >5 mU/L in 7.5, 4.4, 5.6, and 4.3% patients, respectively. TSH decreased significantly (0.17 mU/L) in patients on statins and changed insignificantly in patients on H2 receptor antagonists or glucocorticoids (25).

Before continuing, SB informs that this minireview disregards the endocrine disruptors, and does not emphasize clinically inconsequential IM. Such medications are those listed at the end of **Table 2** (furosemide, heparin, salycylates, and other nonsteroidal anti-inflammatory drugs), which inhibit T4 binding to plasma proteins thus increasing serum FT4, and the unlisted propranolol (20). Also, a number of articles are dedicated to specific IM (26–40).

THYROID DYSFUNCTION AND SUBOPTIMAL TREATMENT CAUSED BY INTERFERING MEDICATIONS OCCUR IN A PROPORTION OF PATIENTS

The Scottish study (25) is important because it reminds that not all L-T4-replaced hypothyroid patients taking IM become undertreated. For instance, a 3-month supplementation of 1,200 mg/d calcium carbonate reversibly increased TSH in 13/20 patients (65%), with TSH >4.0 mU/L in four (20%) (41). Overall, TSH increased from 1.60 ± 0.22 to 2.71 ± 0.43 mU/L (+69%). Calcium carbonate adsorbed T4 dose-dependently at pH 2 but not pH 7.4, thus explaining L-T4 malabsorption (41), and reduced T4 pharmacokinetics (42). Lower L-T4 bioavailability applies to other calcium salts (43). Those data (41) match data of SB (44). Fifty postmenopausal women with L-T4-treated PH started taking 600–1000 mg/d calcium carbonate ≤2 h after L-T4. UTH (TSH >4.12 mU/L) occurred in 9/50 women (18%). Overall, TSH increased from 1.93 ± 0.51 mU/L to 3.33 ± 1.93

TABLE 1 | Recommendations concerning medications that interfere with L-T4 therapy in the latest American Thyroid Association Guidelines on hypothyroidism*.

Year (ref.)	Question and Recommendation
2012 (4)	How should patients with hypothyroidism be treated and monitored?
	26. In patients receiving L-thyroxine treatment for hypothyroidism, serum TSH should be remeasured within 4–8 weeks of initiation of treatment with **drugs that decrease the bioavailability or alter the metabolic disposition of the L-thyroxine dose**.Grade A, BEL 1
	When should endocrinologists be involved in the care of patients with hypothyroidism?
	28. Physicians who are not endocrinologists, but who are familiar with the diagnosis and treatment of hypothyroidism *should be able* to care for most patients with primary hypothyroidism. However, patients with hypothyroidism who fall into the following categories should be seen in consultation with an endocrinologist. These categories are (i) children and infants, […] and (ix) unusual **causes of hypothyroidism such as those induced by agents that interfere with absorption of L-thyroxine, impact thyroid gland hormone production or secretion, affect the hypothalamic–pituitary–thyroid axis (directly or indirectly), increase clearance, or peripherally impact metabolism**.Grade C, BEL 3
2014 (5)	Are there medications and supplements that should not be co-administered with levothyroxine in order to avoid impaired absorption?
	3b. We recommend that where feasible, levothyroxine should be separated from other potentially interfering medications and supplements (*e.g.*, **calcium carbonate** and **ferrous sulfate**). A 4-h separation is traditional but untested. Other medications (*e.g.*, **aluminum hydroxide** and **sucralfate**) may have similar effects but have been insufficiently studied.Weak recommendation. Weak quality evidence.
	What medications may alter a patient's levothyroxine requirement by affecting either metabolism or binding to transport proteins?
	3e. Initiation or discontinuation of **estrogen** and **androgens** should be followed by reassessment of serum thyrotropin at steady state, since such medications **may alter the levothyroxine requirement**. Serum thyrotropin should also be reassessed in patients who are started on agents such as **tyrosine kinase inhibitors** that affect thyroxine metabolism and thyroxine or triiodothyronine deiodination. Serum thyrotropin monitoring is also advisable when medications such as **phenobarbital, phenytoin, carbamazepine, rifampin, and sertraline** are started.
	Strong recommendation. Low-quality evidence.

**Bold-face print is by the author of this minireview, in order to highlight terms and/or parts of interest.*

TABLE 2 | Medications that may interfer on with L-T4 therapy and suggestions for management in addition to monitoring of thyroid function.

Medication	Mechanism(s)	What to do
Antacids, nonabsorbable§	Physical interaction with T4	Concomitant use to be avoided (intake separated by ≥4 h)
Calcium salts§	Physical interaction with T4	Concomitant use to be avoided (intake separated by ≥6 h)
Cholestyramine§, Colesevelam§	Physical interaction with T4	Concomitant use to be avoided (intake separated by ≥4 h)
Phosphate binders§ and potassium binders	Physical interaction with T4	Concomitant use to be avoided (intake separated by ≥4 h)
Ferrous salts§	Physical interaction with T4	Concomitant use to be avoided (intake separated by ≥4 h)
Orlistat§	Physical interaction with T4?	Thyroid function to be monitored.L-T4 dose may need to be increased
Antacids, absorbable§	Increase of intragastric pH	Thyroid function to be monitored.L-T4 dose may need to be increased
Androgens/Anabolic steroids*	↓ both T4 binding to plasma proteins and TSH	Thyroid function to be monitored.L-T4 dose may need to be lowered
Estrogens*	↑ both T4 binding to plasma proteins and TSH	Thyroid function to be monitored.L-T4 dose may need to be increased
Tamoxifen*	↑ T4 binding to plasma proteins	Thyroid function to be monitored.L-T4 dose may need to be increased
Raloxifene *§	↑ T4 binding to plasma proteinsT4 malabsorption	Concomitant use to be avoided (intake separated by ≥12 h)L-T4 dose may need to be increased
Clofibrate*	↑ T4 binding to plasma proteins	Thyroid function to be monitored.L-T4 dose may need to be increased
Fluorouracil* and its prodrug capecitabine*	↑ T4 binding to plasma proteins	Thyroid function to be monitored.L-T4 dose may need to be increased
Corticosteroids*	↓ TSH	L-T4 dose may need to be lowered
Growth hormone	↑ T4 metabolism	Thyroid function to be monitored.L-T4 dose may need to be increased
Antiepileptics (carbamazepine*, phenytoin*, phenobarbital*, valproate, etc…)	↑ T4 metabolism; ↓ T4 binding to plasma proteins and ↓ TSH (phenytoin)	Thyroid function to be monitored.L-T4 dose may need to be increased
Lithium†	↓ T4 synthesis; ↓ T4 metabolism, ↑ TSH	Thyroid function to be monitored.L-T4 dose may need to be increased
Tricyclic antidepressants; SSRIs*	↓ TSH; SSRIs ↑ TSH	Thyroid function to be monitored.L-T4 dose may need to be increased
Rifampin*	↑ T4 metabolism	Thyroid function to be monitored.L-T4 dose may need to be increased
Metformin	↓ TSH	Thyroid function to be monitored.
Sulphonamides	↓ T4 synthesis	Thyroid function to be monitored.
Aminoglutethimide†	↓ T4 synthesis	Thyroid function to be monitored.L-T4 dose may need to be increased
Mitotane*	↑ T4 binding to plasma proteins. ↑ T4 metabolism, ↓ TSH	Thyroid function to be monitored.L-T4 dose may need to be increased
Bexarotene†	↑ T4 metabolism, ↓ TSH	Thyroid function to be monitored.L-T4 dose may need to be increased
Dopamine (≥0.4 mcg/kg/min), dopamine agonists	Transiently ↓ TSH	Change in L-T4 dose unnecessary
Octreotide (≥100 mcg/day), somatostatin analogs	Transiently ↓ TSH	Thyroid function to be monitored.L-T4 dose may need to be increased
Antiretroviral drugs	↑ T4 metabolism	Thyroid function to be monitored.L-T4 dose may need to be increased
Ethionamide†, para-aminosalicylic acid†	↓ iodine organification; thyroiditis	Thyroid function to be monitored.
Thalidomide, lenalidomide, pomalidomide	Thyroiditis	Thyroid function to be monitored.
Tyrosine kinase inhibitors*†	Thyroiditis; ↑ T4 metabolism; inhibition T4 and T3 cell transporters.	Thyroid function to be monitored.L-T4 dose may need to be increased
Cytokines, Interferons†	Thyroiditis	Thyroid function to be monitored.
Monoclonal anti CD52 (alemtuzumab)	Thyroiditis	Thyroid function to be monitored.
Monoclonal anti-CTLA-4 Ab (ipilimumab, tremelimumab)	Hypophysitis; thyroiditis	Thyroid function to be monitored.
Monoclonal anti-PD-1 Ab (nivolumab, pembrolizumab)	Thyroiditis; hypophysitis	Thyroid function to be monitored.
Furosemide	↓ T4 binding to plasma proteins	Change in L-T4 dose unnecessary
Heparin	↓ T4 binding to plasma proteins	Change in L-T4 dose unnecessary
Nicotinic acid	↓ T4 binding to plasma proteins	Change in L-T4 dose unnecessary
Salicylates (>2 g/day) and other nonsteroidal anti-inflammatory drugs	↓ T4 binding to plasma proteins	Change in L-T4 dose unnecessary

Ab, antibody/antibodies; CLTA-4, cytotoxic T lymphocyte-associated antigen 4; PD-1, programmed cell death-1 receptor; SSRIs, selective serotonin reuptake inhibitors.

Symbols: ↑, increased; ↓, decreased. Based on Jonklaas (10), drugs that "may alter the levothyroxine dose required by a patient" are indicated by one asterisk (*) if the mechanism is "by affecting T4 metabolism or transport", and by the section sign (§) if the mechanism is "by affecting levothyroxine absorption". The dagger (†) identifies medications that may trigger hypothyroidism, which is of the central type in the case of bexarotene, and may also be of the central type in the case of medications that act by lowering TSH secretion and causing hypophysitis.

In the literature, interfering medications are categorized variably, depending on mechanism, with some medications having multiple mechanisms. For instance, the 2012 American Thyroid Association (ATA) guidelines (4) considered four mechanistic categories, with information provided when mechanisms are multiple, namely: (i) direct and indirect effects on the hypothalamic–pituitary–thyroid axis; (ii) thyroid gland hormone production and secretion; (iii) increased clearance; (iv) interference with absorption. In the 2014 ATA guidelines (5), categories were two, viz. (i) impaired absorption, and (ii) altered metabolism or binding to transport proteins, with emphasis on the first category. In a book (20) medications are listed under five categories: (i) central TSH inhibition; (ii) absorption; (iii) synthesis and secretion; (iv) transport; (v) metabolism. In another chapter of this book (10), emphasis is given to drugs that may alter the L-T4 dose by affecting (i) T4 metabolism or transport, and (ii) L-T4 absorption. In another book (22), drugs are listed under two major categories, viz. interfering with (i) hypothalamic–pituitary–thyroid function, (ii) thyroid function.

Whenever "thyroiditis" appears in the second column of the Table (Mechanism), the clinical implication is that such silent thyroiditis may translate into monophasic thyrotoxicosis, monophasic hypohyroidism, or biphasic dysfunction (thyrotoxicosis followed by hypothyroidism). However, hypothyroidism may sometimes be permanent. In the case of lithium, a few cases of thyrotoxicosis have been reported. Interferon alpha, alemtuzumab, ipilimumab, tremelimumab, nivolumab and pembrolizumab may even trigger true Graves' disease. Clearly, whenever a L-T4-treated hypothyroid patient experiences increased discharge of thyroid hormones (thyrotoxicosis or hyperthyroidism), because he/she is simultaneously taking a medication that causes such side-effect, L-T4 therapy has to be withdrawn. Upon rechecking thyroid function tests during the follow-up period in such patient, L-T4 replacement is started again.

mU/L (+73%), but when all women took calcium 6–8 h after L-T4, all had TSH <4.12 mU/L (2.16 ± 0.54 mU/L) (44).

Confirming previous data (45), in 37 PH patients under stable L-T4 replacement and in whom PPIs were administered subsequently, TSH increased by 28%, with seven patients (19%) having post-PPI TSH levels >5 mU/L (46). A mean increase of 20 µg/d L-T4 (+35%) was necessary (46).

In 71 L-T4-treated PH patients who started the antituberculosis drug rifampin, an increased L-T4 dose was required for 50% of 46 patients (TSH-suppressive group) and 26% of 25 patients (replacement group) (47). Lack of thyroid remnant, time interval between starting rifampin and TSH measurement, and baseline L-T4 dose/kg body weight were significant risks for UTH (47). Ethionamide and para-aminosalycilic acid (PAS) are used in multidrug-resistant tuberculosis (MDR-TB). After initial reports (48–50), a meta-analysis on 6,241 MDR-TB patients (31) showed that PH prevalence in MDR-TB patients averaged 17.0%, with ethionamide and PAS were the most frequently reported drugs associated with hypothyroidism. Tubercolosis is a common opportunistic infection in HIV-seropositive persons, and antiretroviral therapy (ART) may induce PH. Of 69 HIV-infected MDR-TB patients under anti-TB and antiretroviral therapies, 37 (54%) had PH (51). Co-administration of PAS and ethionamide doubled the risk of hypothyroidism (RR = 1.93) (51). In MDR-TB patients receiving anti-TB, one-fourth developed PH: 32% in patients who received a regimen containing ethionamide, 35% in patients who received a regimen containing PAS, and 44% in HIV-positive patients on ART (52).

Immune reconstitution therapy (IRT)-induced either autoimmune hyperthyroidism with/without ophthalmopathy or autoimmune hypothyroidism may occur following: (i) highly active antiretroviral therapy (HAART) of HIV infection, (ii) alemtuzumab treatment for active relapsing-remitting multiple sclerosis, and (iii) allogeneic bone marrow transplantation or hematopoietic stem cell transplantation (30). No recommendation for managing IRT-related thyropathies addressed possible changes in L-T4 doses (30). Hypothyroid HAART-treated patients needing increased L-T4 doses were reported (53–55). HAART drugs were ritonavir (48), abacavir–lamivudine and lopinavir–ritonavir (54), and lopinavir/ritonavir plus zidovudine and lamivudine (55). Switch from lopinavir/ritonavir to nelfinavir failed to achieve euthyroidism (55), which was restored when dolutegravir was substituted for lopinavir–ritonavir (54). However, 826 well-treated HIV-infected persons, 95% of whom with undetectable viral replication, did not differ from 2,503 uninfected controls for prevalence of hyperthyroidism (0.8 *vs.* 0.8%) or hypothyroidism (3.8 *vs.* 4.6%) (56).

Hypothyroidism occurs in around 20 or 5–10% of thalidomide- or lenalomide-treated patients (57, 58). Of 170 patients under lenalidomide, 6% had thyroid dysfunction (hypothyroidism > thyrotoxicosis), which prevailed in patients with known *vs.* unknown thyroid dysfunction (17 *vs* 6%) (58). Unfortunately, the article fails to specify how many patients were under L-T4 and how many needed increased L-T4 doses (58). With just two cases reported (59, 60), the rate of pomalidomide-induced hypothyroidism is unknown. Interestingly, thyroid hormone autoantibodies appeared in 14% of thalidomide or lenalidomide-treated patients (61).

Autoimmune thyroiditis is also caused by monoclonal Ab to programmed cell death-1 receptor (nivolumab and pembrolizumab), and Ab to cytotoxic T lymphocyte-associated antigen-4 (ipilimumab, tremelimumab) (27, 37–39). Rates of hypothyroidism are 0–40% (nivolumab), 0–11.5% (pembrolizumab), 0–9% (ipilimumab), and 0–5% (tremelimumab) (38).

Tyrosine kinase inhibitors (TKI) may cause *de novo* hyperthyroidism or hypothyroidism, or worsen pre-existing hypothyroidism and increase L-T4 requirements (27–29). Upgraded titration of L-T4 was reported in athyreotic patients prescribed imatinib, motesanib, sorafenib, sunitinib, and vandetanib (5, 62, 63). Nilotinib and dasatanib rarely alter L-T4 requirements (27). One mechanism for the L-T4 increased requirements, further to T4 increased metabolism, can be inhibition of MCT8-dependent T3 and T4 uptake (64), since MCT8 is expressed by the gastrointestinal tract (65).

Other anti-cancer IM are mitotane (see below) and aminogluthetimide, a first-generation aromatase inhibitor used for advanced breast cancer (ABC), but whose side-effects and need for concomitant hydrocortisone limited its utility (66). Of 29 aminoglutethimide-treated patients with prostate cancer, nine (31%) developed hypothyroidism (TSH >10 mU/L) (67). Of 32 women under aminoglutethimide + hydrocortisone for ABC, 17 (53%) had hyperthyrotropinemia before treatment. In 15/17 patients, TSH increased further, with seven developing OH (68). Because aminoglutethimide blocks adrenal steroidogenesis, it is used to treat Cushing's syndrome (69).

OH or SCH develop in up to 15 or 34% of lithum-treated patients (20), the annual rate of developing PH being 1.5%, (6.4% in thyroid antibody-positive and 0.8% in thyroid antibody-negative individuals) (70). Women <60-year-old are at greatest risk to develop thyroid disease (71). Indeed, women develop OH or SCH three times more frequently than men (25.8 *vs.* 8.7%), with prevalence among women exceeding 50% by the age of 65 years (35). During tricyclic antidepressant therapy, TSH levels are unchanged, and T4 and FT4 levels decrease within the euthyroid range, though other studies reported unchanged thyroid function tests (TFTs) (72). Selective serotonin reuptake inhibitors (SSRIs) affect TFTs variably, usually with no or downward changes of FT4 and FT3, and no or upward change of TSH within the corresponding reference range (72). L-T4 requirements increased in nine L-T4-treated hypothyroid patients under sertraline (73). Confirming the sertraline-T4 interaction, in two patients under TSH-suppressive L-T4 therapy, TSH levels rose into the normal range (73). A 3-month duration study was conducted in 57 patients with major depression and 10 control patients (72). The study patients were hypothyroid on adequate L-T4 therapy (n = 28) who were randomized to fluoxetine (n = 13) or sertraline (n = 15), and euthyroid (n = 29) who were treated with fluoxetine (n = 15)

or sertraline (n = 14). Controls had hypothyroidism on adequate L-T4 therapy without depression (72). No changes occurred in the L-T4-replaced hypothyroids under either SSRI. In response to a letter (74) commenting that difference with the early study (73) could be that" *many … patients … were athyreotic*", the authors admited that "*in most [patients] the cause of hypothyroidism was autoimmune*" (75). Noteworthy, a 41-year-old man with a history of bipolar disorder and schizophrenia had myxedema coma after therapy with sertraline and ariprazole (76). After discharge, TSH remained high (34 IU/ml) on sertraline, ariprazole and 200 μg/d L-T4.

SCH may occur reversibly following administration of antiepileptic drugs (AED), particularly carbamazepine, phenytoin, valproate (77), oxcarbazepine, but not lamotrigine, levitracetam, tiagabine and vigabatrine (36). AED administration in L-T4-replaced patients with either PH (78) or CH (32) requires higher L-T4 doses.

The anti-obesity drug orlistat inhibits gastro-intestinal lipases and is minimally absorbed. Based on data of the UK Medicines Information pharmacists (79), only two cases of interaction between orlistat and L-T4 were reported (80, 81), most likely *via* T4 malabsorption. It was recommended that L-T4 and orlistat "*should be separated by 4 hours, and increased monitoring of […] thyroid hormone levels may be prudent*" (79).

Through acceleration of both thyroid hormone and cortisol metabolism, initiation of growth hormone (GH) replacement may unmask CH and hypoadrenalism (82–84). Also, patients already under L-T4 replacement need increased L-T4 doses (82, 84). Unmasking of CH and increased L-T4 doses occurred in 30/84 (36%) and 25/159 (16%) patients, respectively (84).

A single oral dose of clofibrate decreased significantly hyperthyrotropinemia of PH patients (87). Clofibrate did not change discernibly basal and TRH-induced TSH secretion in euthyroids. Similar results were given by meclofenoxate hydrochloride (87), suggesting that both drugs inhibit TSH secretion in PH patients possibly acting on the hypothalamus/pituitary (87). Clofibrate also increased serum T4-binding capacity of TBG, lowering serum FT4 in 11/12 hyperlipoproteinemic patients (92%) (88).

The adrenocytolytic drug mitotane is used to treat adrenocortical carcinoma (ACC) (89). In 17 patients with radically resected ACC, mitotane was administered associated with glucocorticoid replacement therapy (90). Excluding three patients under L-T4 treatment and one with SCH, during the first year, FT4 became subnormal in 12/13 evaluable patients (92%), with L-T4 replacement started after 9 months in four. At last follow-up, FT4 levels were unchanged compared with the 12 month-evaluation, but another three patients needed L-T4 replacement. Five women with mitotane-treated ACC showed features of CH, namely low FT4, normal FT3 and TSH, with impaired TSH response to TRH (91). Mitotane increased serum FT3/FT4 ratio, suggesting enhanced T4 to T3 conversion, a compensatory mechanism of hypothyroidism (91). CH was reported in a girl with mitotane-treated ACC (92); full restoration of FT4 required increasing the L-T4 dose. After completing chemotherapy, TFTs remained normal, and L-T4 replacement was discontinued.

The retinoid bexarotene causes CH in almost all patients (22), *via* TSH suppression (93) and non-deiodinase-mediated thyroid hormone increased metabolism (94).

PHARMACOLOGICAL INTERFERENCE AT CENTRAL LEVEL

The antipsycotic dopamine antagonists (*e.g.*, phenothiazines, haloperidol, domperidone, metoclopramide, cimetidine), antidepressive tricyclics and α-methyldopa slightly increase serum TSH without altering thyroid function (17). Though dopamine and its agonists (bromocriptine, cabergoline), somatostatin analogs (octreotide), dobutamine, amphetamines and corticosteroids inhibit TSH, patients taking chronically these medications have no sustained decreases of TFTs. Consequently, CH does not develop (34, 85). Reversible inhibition of TSH secretion is also observed with AED, particularly phenytoin (20).

Anti-CTLA-4 Ab and anti-PD-1 Ab induce autoimmune hypophysitis (27, 37–39), with rates of 0–17.4% (ipilimumab), 0–2.6% (tremelimumab), 0–0.9% (nivolumab), and 0–1.2% (pembrolizumab) (38). In anti-CTLA4-Ab-induced hypophysitis, ACTH- and TSH-deficiency are frequent (38).

Metformin lowers serum TSH in L-T4-treated OH and L-T4-untreated SCH patients, but not in euthyroid patients (33). After its chronic administration, FT4 was unchanged and TSH decreased in L-T4-treated or L-T4-untreated hypothyroid diabetics, but not in euthyroid subjects (86).

HYPOTHYROID PATIENTS HOSPITALIZED IN INTENSIVE CARE UNITS (ICU)

Among 133 such patients, TFTs were not performed in 29 (21.8%), replacement therapy was not prescribed for >7 days in 23 (17.3%) and was omitted in three (2.2%) (95). Nine hypothyroid patients who stayed at ICU for 12–45 days received H2-blockers as routine prophylaxis against gastroduodenal bleeding and were nasogastrically fed a calorically dense solution (96). This solution was stopped 2 h before and resumed 2 h after L-T4 administration (crushed tablets) nasogastrically. After the first 4–8 days at ICU, with L-T4 doses unchanged, TSH of all patients increased significantly to 5.69 mU/L (IQR = 3.87–6.83) from 1.52 mU/L (IQR = 0.79–3.8) at admission. L-T4 dose was increased in 8/9 patients (88.9%) from 86.1 ± 41.6 to 125 ± 39.5 μg/d (54.4 ± 31.6%). Upon discharge, TSH returned to levels (2.8 mU/L [IQR = 1.4–5.5]) insignificantly different from baseline. The increased L-T4 requirements were attributed to increased gastric pH by H2-blockers (and subsequent decreased L-T4 absorption) and increased T4 to reverse-T3 shunting (due to enhanced type-III deiodinase activity during critical illnesses) (96). In 320 ICU patients, the most frequent clinically significant drug–enteral

nutrition interactions concerned phenytoin, warfarin and L-T4 (97).

CURRENT RESEARCH GAPS

Concerning IM-induced UTH, few data are available on two issues (23, 44, 98, 99): (i) metabolic/cardiovascular complications, (ii) costs of frequent assays to monitor L-T4 therapy.

In the aforementioned study on 114 L-T4-treated PH patients (23), exposure to IM (32.1 ± 6.9 months) significantly increased TSH from 1.27 ± 1.34 to 2.81 ± 3.62 mU/L (+121%), and proportions of TSH >4.12 mU/L from 4.7 to 18.5% and >2.50 mU/L from 20.2 to 53.5% compared to the non-exposure period (35.4 ± 9.7 months). Some complications ensued: aggravation of pre-existing or *de novo* onset of any of metabolic syndrome (MS), impaired fasting glycemia (IFG), diabetes, dyslipidemia, hypertension, cardiovascular disease (CVD). Seventy-six patients (67%) had complications, whose rates of TSH >4.12 or >2.50 mU/L were significantly greater than in the 36 complication-free patients (22 *vs.* 11%, or 35 *vs.* 17%). TSH in patients with complications *vs.* complication-free patients were 118% greater during exposure (3.44 ± 4.08 *vs.* 1.58 ± 1.98 mU/L) (23). In the above study on 50 postmenopausal L-T4-treated PH women (44), TSH increased significantly from 1.93 ± 0.51 (before calcium; setting 1) to 3.33 ± 1.93 mU/L (calcium taken ≤2 h after L-T4; setting 2), and was significantly lower than 2.16 ± 0.54 mU/L (calcium taken 6–8 h after L-T4; setting 3). Total cholesterolemia (TC), fasting glycemia (FG), systolic and diastolic blood pressure (SBP and DBP) were also significantly higher in setting 2 *vs.* settings 1 and 3. For every 1.0 mU/L increase within the TSH range of 0.85–6.9 mU/L, TC, FG, SBP, and DBP increased by 12.1 mg/dl, 3.12 mg/dL, 2.31 mmHg, and 2.0 mmHg, respectively (44). As summarized elsewhere (100), our data (23, 44) agree with other data outside of the IM setting, which show that as TSH levels increase within its euthyroid range, metabolic and cardiovascular outcomes worsen progressively. For instance, comparing TSH of 3.0–3.5 mU/L with 0.50–0.99 mU/L, the OR for hypertension was 1.98 in men and 1.23 in women (101). Within the reference range of 0.50–3.5 mU/L, blood pressure increased linearly with increasing TSH (SBP by 2.0 mmHg in men and 1.8 mmHg in women, DBP increased by 1.6 and 1.1 mmHg) (101). In 12,584 adults with normal TSH levels, the frequency of diabetes, hypertension, and hypercholesterolemia, increased significantly across TSH tertiles (diabetes = 6.3, 7.7, and 9.1%; hypertension = 20.9, 24.8, and 29.8%; hypercholesterolemia = 13.2, 15.2, and 19.4%) (102). Moreover, SCH might favor diabetic complications with an OR of 1.74 (nephropathy), 1.42 (retinopathy), 1.85 (peripheral arterial disease), and 1.87 (peripheral neuropathy) (103).

High-normal TSH levels impact unfavorably on mortality. In 9,020 adults, SCH (TSH >5.60 mIU/L) and high-normal TSH (1.96–5.60 mIU/L) were associated with increased all-cause mortality (HR = 1.90 and 1.36) *vs.* the middle-normal TSH group (1.20–1.95 mIU/L) (104), with CVD mediating 14.3 and 5.9% of the association, respectively (104). A study on 611 hospitalized elderly patients evaluated all-cause mortality up to 66 months after discharge (105) and concluded that (i) in treated hypothyroid patients, median TSH levels of 5–10 IU/L associated with increased mortality, (ii) treatment should aim at achieving euthyroidism to improve survival (105).

Undertreated CH is associated with increased weight, BMI, larger waist circumference (106), and higher fat mass, worse lipid profile (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides) (107), with increased risk for cardiovascular morbidity (108).

Concerning costs, these were estimated by four simulations, based on 5% rate of PH (4.5% SCH, 0.5% OH), three rates (10, 50, and 80%) of L-T4-treated SCH patients, 440,000 to 3,608,000 UTH persons, and a total of 125,800 to 1,031,888 persons with calcium-related UTH and iron-related UTH (98). At euro 20 for one TSH test, the total cost for five TSH tests in these 125,840 or 1,031,888 patients ranged euro 12,584,000 to 103,188,800. Another study (99) analyzed the cost of resources consumed by frequent L-T4 dose changes over 24 months (laboratory testing, thyroid medications, general physician and specialist office visits, and emergency department visits/hospitalizations) in two groups of 227 hypothyroids each. Compared with the no-dose-adjustment patients (controls), significantly more patients needing dose adjustments (75 *vs.* 86%), were taking IM causing L-T4 malabsorption (PPIs, H2-receptor antagonists, calcium or iron supplements) (99). Overall resource utilization was higher in the ≥1-dose-adjustment group ($5,824/patient) *vs.* controls (USD 3,166/patient), peaking in the ≥3-dose-adjustment subgroup ($8,220/patient). The ≥1-dose-adjustment group experienced a 40.3% increase in lost productivity *vs.* controls ($1,381 *vs.* $984), with a peak in the ≥3-dose adjustment subgroup ($1,833). Compared to controls, patients requiring adjustments had significantly higher TSH (5.07 ± 11.04 *vs.* 2.57 ± 2.51 U/ml), and more frequent TSH tests (84 *vs.* 73%) (99).

POTENTIAL FUTURE DEVELOPMENTS

In the "Areas for future research" heading of the 2012 ATA guidelines (4), a section was devoted to "*Agents and conditions having an impact on L-thyroxine therapy and interpretation of thyroid tests*". Except for reminding that the residual functioning thyroid tissue is a major factor for a given IM to cause thyroid dysfuntion and L-T4 dose adjustments, no ideas were presented (4).

Future developments have already occurred considering the availability of L-T4 formulations (liquid, softgel) that are refractory or much more resistant to IM than tablet L-T4 (9, 14, 98, 100, 109–114). In the author's opinion, their use seems preferable to the strategies of (i) increasing stepwise the dose of L-T4 (with associated frequent monitoring of TFTs and risk of iatrogenic thyrotoxicosis if the IM is decreased in dose or withdrawn); (ii) adding supplementation with either 1 g/d (115) or 0.5 g/d (116) vitamin C to acidify the intragastric pH. In the Argentinian study, the 28 patients had no known cause for

UTH (115), while in the Colombian study, the 31 patients had endoscopy/gastritis-proven gastritis (116). Both 2-month-long trials with vitamin C (115, 116) lack formal pharmacokinetics studies and challenge of patients with IM-associated UTH. Indeed, coadministration of acidic beverages is one way of solving the problem of decreased bioavailability of drugs whose bioavailability under conditions of increased intragastric pH (117). Further to T4, there are a number of other drugs with decreased absorption at high intragastric pH, such as ketoconazole, itraconazole, atazanavir, cefpodoxime, enoxacin, dipyridamole, raltegravir, alendronate, digoxin, and nifedipine, to name a few (117). The other way is the development of "*formulations that can minimize or mitigate the effects of increased gastric pH on the bioavailability*" (117).

Considering the magnitude of polypharmacy, particularly in the elderly (118), and the aforesaid unfavorable impact of UTH on metabolic and CVD outcomes, more research is needed to substantiate those outcomes in the setting of IM-associated UTH. Once pejorative outcomes are confimed, monitoring of hypothyroid patients under IM should be tightened, with the biochemical monitoring not restricted to TSH solely.

AUTHOR CONTRIBUTIONS

SB made the work, drafted the article, revised it, and gave the final approval for the publication.

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Levothyroxine Therapy in Gastric Malabsorptive Disorders

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Oral levothyroxine sodium is absorbed in the small intestine, mainly in the jejunum and the ileum being lower the absorption rate at duodenal level. The time interval between the ingestion of oral thyroxine and its appearance in the plasma renders unlike a gastric absorption of the hormone. However, several evidence confirm the key role of the stomach as a prerequisite for an efficient absorption of oral levothyroxine. In the stomach, in fact, occur key steps leading to the dissolution of thyroxine from the solid form, the process bringing the active ingredient from the pharmaceutical preparation to the aqueous solution. In particular, gastric juice pH, volume, viscosity, as well as gastric emptying time seem to be the most important limiting factors. These hypotheses are confirmed by the detection of an increased need for levothyroxine in patients with *Helicobacter pylori* infection, chronic atrophic gastritis, gastroparesis, or in simultaneous treatment with drugs interfering with gastric acidic output. The aim of the present article is to focus on the knowledge of pathophysiologic events that determine the absorptive fate of traditional (tablet) and alternative thyroxine preparations (softgel capsule and liquid solution) in patients bearing gastric disorders.

Keywords: hypothyroidism, levothyroxine, malabsorption, *Helicobacter pylori*, proton pump inhibitors, gastritis, liquid levothyroxine, softgel levothyroxine

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INTRODUCTION

Levothyroxine sodium monotherapy is usually prescribed as treatment in replacement mode for hypothyroid patients worldwide (1). The need for an individually tailored dose has been strongly suggested (2). However, a significant number of patients fail to show a biochemical and/or clinical response and larger doses of thyroxine are required to reach the target serum TSH concentrations (3). Long-term suboptimal treatments have detrimental effects on body homeostasis (4). Frequent changes of dose and repeated diagnostic procedures in these patients have been related to incremental health costs (5). The causes of an increased thyroxine requirement have been recently reviewed (6). Among these, the role of the altered gastric physiology on the subsequent intestinal T4 absorption has been repeatedly highlighted (7–9). The mechanism by which intestinal absorption of thyroxine is impaired in patients with gastric disorders is unclear but seems to pertain to the chemical and physical properties of both naïve and salificated thyroxine molecule (10). Levothyroxine, the levo-isomer of thyroxine, is insoluble in water and in other usual organic solvents (11). The salification process by a saturating excess of sodium hydroxide leads to the

sodium salt production that is the compound used in every pharmaceutical preparation of thyroxine (12). The oral is the preferred route of administration, due to safety and patients' preference (13). Oral levothyroxine absorption is incomplete with reported percentages of about 70% of the administered dose (14). The actual site of absorption is represented by the jejuno-ileal tract while only a few part of oral thyroxine is absorbed in the duodenum (14). Unlike the rat, no absorption in the large bowel has been described in humans (15). Furthermore, the study of the lag time between thyroxine ingestion and its appearance in the plasma excludes the possibility of absorption occurring in the stomach (15). However, several clinical studies suggested that the variations of gastric physiology might have a deep impact on oral thyroxine bioavailability, leading to an increased need for the drug. We aimed at reviewing the known and unknown on the role of the gastric environment in the absorption of oral thyroxine.

GASTRIC CONTRIBUTION TO DRUGS BIOAVAILABILITY

Most of the drugs are absorbed at intestinal level. This assumption is based on its large surface extension and on the presence of different transporters on mucosal membrane (16). Absorption by duodenal mucosa is in turn regulated by its integrity, motility, mucus composition, and resident microbial population (16). On the contrary, drugs absorption from the stomach is usually thought to be negligible, although a passive diffusion through the gastric wall has been hypothesized and proven for compounds such as ethanol and small neutral molecules (16). The gastric absorption seems to be related to the ionization status of the drug that, in turn, depends on the gastric juice pH: in fact, in an acidic environment, acidic drugs are mainly present and absorbed in a unionized form, being this process negligible for basic drugs (17). However, because of the paucity of papers on this topic further studies are warranted. Anyway, the gastric environment exerts profound effects on drugs behavior and pharmacokinetic. In fact, several steps must be taken into account when analyzing the so-called "gastric phase," which represents a pivotal prerequisite for the intestinal drug absorption (16). Once reached the stomach, the drug undergoes disintegration, dissolution, and possible precipitation; furthermore, the active ingredient must reach the actual site of absorption. Disintegration causes the release of the active ingredient from the solid form. The duration of this step is highly affected by the type of the formulation and by the excipients used (tablets, capsules, immediate-release formulations), the fasted or fed state, the gastric residence time, and the gastric motor function (16, 18). Simultaneously, the dissolution of the drug occurs. The dissolution process consists in the release of solute molecules from the solid phase to the liquid one, represented by the gastric juice. Again, this process may be affected by physicochemical characteristics of the drug (e.g. particle size and polymorphisms) and by physicochemical conditions (19) on which the role of gastric juice pH and viscosity stand out (20). Several drugs (21), including levothyroxine, share these processes (**Figure 1**).

LEVOTHYROXINE STRUCTURE

The shared characteristic of all thyroid hormones is the thyronine nucleus, a diphenyl ether in which the two planar phenyl groups are oriented at an angle of 120 degrees (10). Four iodine substituents at the 3,5,3′ and 5′ positions and the presence of 4′ hydroxyl group in the outer ring characterize thyroxine molecule. Interestingly, the inner ring contains an alanine side chain, which, at physiologic pH, is usually zwitterionic (i.e., net positive charge at the amine group and net negative charge at carboxylic oxygen atoms). Thus, in the thyroxine molecule, three ionizable moieties exist, two acidic (the carboxylic and the phenolic one) and one basic aminic group possessing three distinct pK_a (10). It follows that thyroxine may exist in four different ionization status such as zwitterionic, predominant in the range of pH between 2.46 and 6.91 as well as cationic, anionic, and dianionic predominating at more extreme pH (6, 11) depending on environmental pH. The most common pharmaceutical form is the pentahydrated sodium salt of T4 (22). Mondal et al. (23) have shown that almost two polymorphs of levothyroxine do exist. These authors proved the existence of two crystal structures of T4, whose behavior in solution significantly differs being not comparable in different medium pH. The authors hypothesized that these changes in the pH-dependent solubility might affect the oral availability and absorption of this drug (23). The overall aqueous solubility of levothyroxine sodium at 25°C decrease from medium pH 1 to 3, then reaching a nadir level until pH 7, level that correspond to a new increase of T4 solubility (24). The solubility is together with permeability the basis of the Biopharmaceutics Classification System (BCS) (25). Based on the solubility and the permeability rates high or low, drugs are in fact classified into one of four categories of the BCS. This has been proven difficult for levothyroxine sodium since there are sources classifying it as belonging to each of the abovementioned classes (26, 27). Interestingly, also the formation of large aggregates in aqueous media may enable the compound to reach concentration even higher than 15 mg/100 ml (26).

INTERFERENCE WITH THYROXINE EFFECTIVENESS ACTING AT GASTRIC LEVEL

Food and Drugs

Several drugs and foods have been proven to interfere with the oral thyroxine absorption [see for rev (6, 28, 29)]. The mechanisms described seem to affect each step of oral and thyroxine absorption and metabolism and are chiefly exerted: a) by changing the gastric pH or adsorbing thyroxine in the stomach; b) by a possible competition with intestinal transporters or adsorbing thyroxine at the intestinal level; c) by affecting thyroxine binding on plasmatic proteins; d) by modulating catabolic thyroxine processes (6, 28). The first two mechanisms are associated with an increased need for thyroxine and are shared by some interfering foods (6). Food itself may represent a gastric hindrance to the bioavailability of drugs

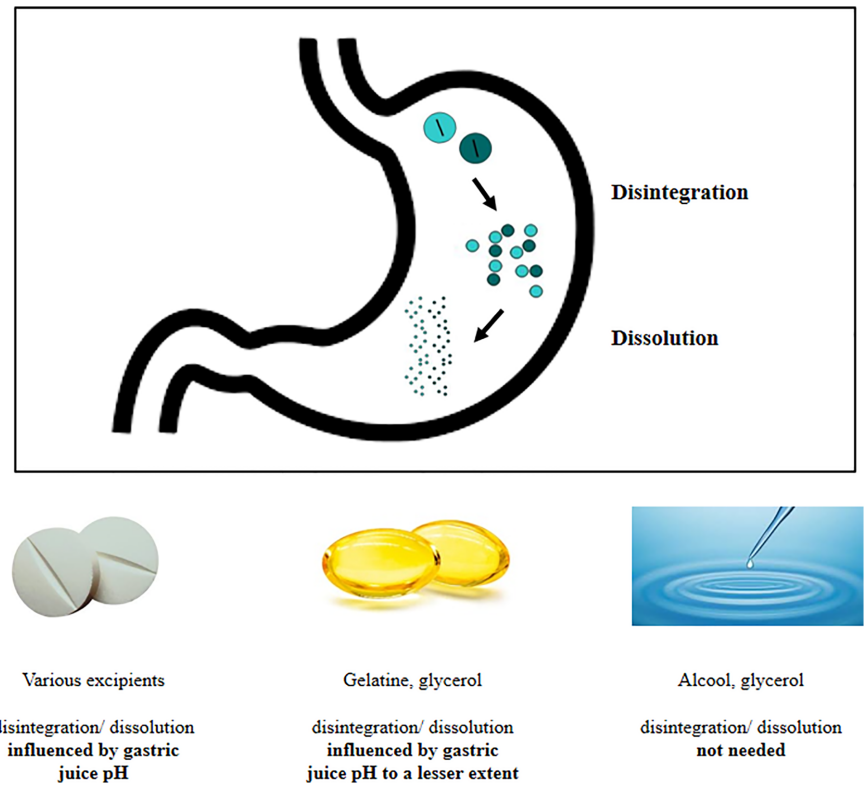

FIGURE 1 | Delivery of active ingredient at gastric level: behavior of different thyroxine formulations.

(30), including thyroxine (31). In clinical practice, the timing of food intake and the interval before and after thyroxine ingestion seems not negligible for the subsequent intestinal absorption (31, 32).

As mentioned above, the mechanisms of interference affecting oral thyroxine during the gastric passage are substantially the variations of gastric juice pH and the binding of thyroxine in an acidic environment. The antacids represent one of the most prescribed categories of drugs worldwide: the interference with thyroxine bioavailability has been described for proton pump inhibitors and calcium carbonate (28). The effect of proton pump inhibitors (PPI) seems to be related to their role in increasing gastric juice pH that might impact on disintegration and dissolution phases of tablet thyroxine (see for rev ref. 6), although their effect on thyroxine absorption kinetics was denied by other authors (33, 34). However, the net effect of PPI on levothyroxine pharmacokinetic is more complex and partially due to the complex variations of gastrointestinal physiology that may be restricted to the long-lasting use of PPI (i.e. variations in gastric mucus viscosity, gastric and small intestinal bacterial overgrowth) (35). Singh et al. (36) reported that both acute and chronic ingestions of calcium carbonate, as well as different preparations of calcium, are able to reduce the bioavailability of T4. Calcium carbonate showed a specific ability to bind thyroxine *in vitro*: indeed, it appears to bind thyroxine in a dose-dependent manner when medium pH is two; this binding disappears when the medium pH is 7.4, preventing absorption at the intestinal level (36). The negative impact of some nutrients on levothyroxine absorption has been demonstrated since 1977 (37). Most of nutrients (e.g. soy, fiber-enriched alimony and coffee, etc.) (6, 38, 39) specifically bind oral thyroxine at the intestinal level. Interestingly, however, some of them seem to interfere with thyroxine absorption at gastric level like the fruit of papaya. The specific action of papaya seems to act even at gastric level since this fruit causes a significant reduction in histamine-induced acid secretion (40). Milk ingestion seems to interfere with thyroxine absorption for its protein and calcium content as well as for its alkaline pH (41). Noticeably, most of antacid drugs may reduce the acidic exposure of thyroxine in the stomach but they also adsorb the hormone in the upper intestinal tract (6).

Gastric Disorders and Surgical Procedures

From a clinical standpoint, the association between gastric and thyroid disorders is very frequent (42). An increased need for thyroxine in patients with gastric disorders has been described in patients with *Helicobacter pylori* infection, chronic atrophic gastritis, in those who underwent gastric surgery or bearing gastroparesis. Among these, *Helicobacter pylori* infection is the most important since its prevalence has been estimated worldwide at 48%, despite wide regional discrepancies (Oceania 24% *vs* Africa 79%) (43). From its discovery in 1982 by Warren and Marshall, the role of *Helicobacter pylori* as cause of inflammatory gastritis in

more of 90% of the cases has become clear (44). Usually, *Helicobacter pylori* related gastritis initially involves the superficial layer of antrum mucosa of the stomach with an inflammatory mononuclear and plasma cells infiltrate. This phase of infection may feature an increased gastrin level and increased gastric juice acidity as well (45). Depending on cytotoxicity of bacterial strain and gastric environment characteristics, the degree of gastritis may get worsened up to atrophic pangastritis and intestinal metaplasia, determining hypo to achlorhydria (44). A role of *Helicobacter pylori* infection in impairing oral levothyroxine bioavailability was firstly described in 2006 (7). In this report and in the one by Bugdaci (46), the increased need for levothyroxine was reversed following *H. pylori* eradication. This latter paper also highlighted the possibility of iatrogenic thyrotoxicosis, maintaining the previous doses of thyroxine after the removal of infection (46). Undiagnosed or persistent *H. pylori* infection has been also proposed as a trigger for autoimmune atrophic gastritis (47, 48) through a molecular mimicry with epitopes of H_+/K_+ATPase, the acid-producing pump of gastric parietal cells (48). In fact, autoimmune chronic gastritis shows a very high degree of corpus and fundus atrophy of the stomach also featuring positive autoantibodies against parietal cells and/or intrinsic factor (49, 50). This pathologic entity is frequently associated with autoimmune thyroid disorders (42, 51), being this association one of the most frequent cases of polyautoimmunity (42, 52). Thyroid and gastric autoimmune disorders are characterized by the action of environmental triggers on genetic predisposing background, leading to the loss of self-tolerance i.e. of the balance between pro- and anti-inflammatory effector cells pathways (52, 53). The co-presence of thyroid and gastric autoimmune disorders features specific immunoregulatory cytokine profiles (54, 55). Autoimmune atrophic gastritis is characterized by achlorhydria and thus by a high oral levothyroxine requirement (7) being maximal in patients bearing the co-presence of gastric atrophy and *Helicobacter pylori* infection (7). The prevalence of autoimmune atrophic gastritis, which is often underdiagnosed, has been estimated as 0.5–5% (51). Achlorhydria is also a feature of laparoscopic sleeve gastrectomy (SG), the most common bariatric procedure performed in the USA (56, 57). The procedure implies the tubulization of the stomach between 50 and 200 cc in volume while the remaining part of the stomach is removed (27). Despite most of the studies examining thyroxine requirement in SG patients described an unchanged or decreased dose of thyroxine needed by patients, the normalization by body weight clearly indicated an increased need for the hormone following this bariatric procedure (56, 57). Patients undergoing bariatric surgery are often advised to use PPIs and micronutrients that may interfere with the absorption of thyroxine; furthermore, their increased need for oral levothyroxine may be warranted by the variations in volume, acidic output, and motility of the remaining part of the stomach (27). These patients, in fact, often show an acceleration of gastric emptying that may impair the disaggregation and dissolution of tablet levothyroxine (58). To note, an increased need for oral levothyroxine has been described in patients with the opposite motility disorder, i.e. gastroparesis (59, 60). However, its frequency is low and estimated in 9/100,000 men and 38/100,000 women (43).

HOW TO SUSPECT GASTRIC DISORDERS AFFECTING LEVOTHYROXINE ABSORPTION

Three main features may led to suspicion of a gastric disorder: clinical symptoms, malabsorption of drugs and micronutrients, and the presence of a chronic unexplained anemia (6). Despite the narrow therapeutic index, empiric and not targeted doses were widely used without proper characterization for long time (3). On the contrary, an essential prerequisite to detect gastric malabsorption is a careful tailoring of patient's treatment devoted to find the minimal effective dose of thyroxine (6). Several characteristics of patients and their habits should be evaluated as shown in **Figure 2**. The timing of thyroxine ingestion represents a primary issue to obtain the therapeutic target using the lowest effective dose (7, 31, 32, 61, 62). Other relevant characteristics are the lean body mass or the body mass index, age, reproductive status, and the absence of bias. An accurate pharmacologic anamnestic investigation is, in fact, mandatory to avoid bias from widely used drugs and/or interfering foods (6, 28, 63, 64). Once excluded all these putative biases, a gastrointestinal

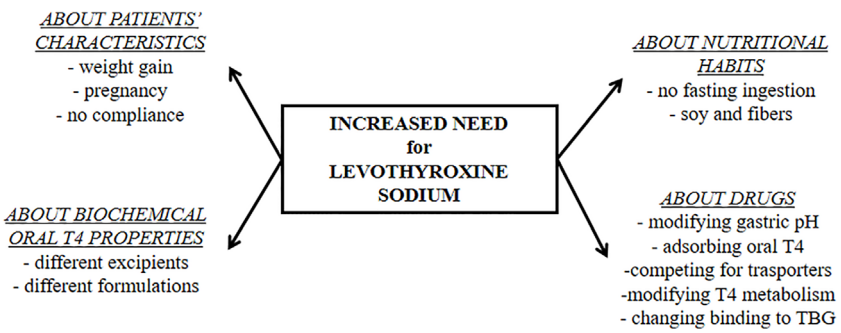

FIGURE 2 | The physiologic and pharmacologic biases of oral levothyroxine treatment that must be excluded before starting a diagnostic workup for malabsorptive disorders.

malabsorption of thyroxine may be suspected (6). The concomitant presence of a macro- or microcytic anemia strengthens the hypothesis of a gastric problem (65, 66). A recent study observed that about half of patients with gastric atrophy presented with anemia that was already severe at the time of diagnosis in one patient out of five (66). Atrophic gastritis is a prevalently silent disease that progresses from a mild chronic gastric inflammation to an advanced stage of atrophy and metaplasia (42). Anemia follows this worsening, proceeding from iron-deficient microcytic phenotype to vitamin B_{12} deficiency-associated macrocytic anemia (pernicious anemia) (65, 66). This latter is a consequence of vitamin B12 malabsorption in turn due to intrinsic factor deficiency (66) whereas the reduced gastric acid secretion lowers iron absorption in iron-deficient anemia (65). Some of these characteristics may prompt a screening for gastrointestinal disorders. The screening for these associated disorders has been recently described and reviewed (6).

At gastric level, the presence of specific antibodies against parietal cell and against *H. pylori* are reliable markers of suspicion as is for fasting gastrin levels. However, the diagnosis of superficial or atrophic gastritis must be based on multiple biopsies and histological examination (42).

THE USE OF NOVEL FORMULATION IN THYROXINE INCREASED NEED DUE TO GASTRIC DISORDERS

The suboptimal efficiency of treatment worldwide (4) prompted industry to develop novel preparations of sodium levothyroxine. Recently, novel formulations of levothyroxine sodium have been introduced: the soft gel capsules and the liquid solution (67). In the softgel capsules, levothyroxine is dissolved in glycerin and surrounded by a gelatin shell while, in the liquid solution, the hormone is dissolved in 95% ethanol and 86% glycerol (**Figure 1**).

A seminal *in vitro* study analyzed the dissolution at different medium pH of two tablet formulations (one brand and one generic) as compared to a softgel capsule (68). The latter performed better at medium pH >3, at which the dissolution curve of the levothyroxine sodium tablet clearly drops (24, 68). A pharmacokinetic study demonstrated that, in healthy subjects and in fasting conditions, softgel capsule formulation is bioequivalent to tablet thyroxine (69).

The dissolution time of the softgel capsule preparation has been directly observed during an endoscopy session in a healthy volunteer, demonstrating that the capsule completely disappeared 21 min following its ingestion (70). Even when analyzed in patients bearing disorders or using drugs increasing gastric juice pH, the softgel formulation performed better than the traditional one (9).

The better performance of softgel formulation in maintaining target TSH levels, despite a lower dose as compared to the tablet one, has been demonstrated in most of the patients bearing superficial gastritis, gastric atrophy, and resistant-to-treatment *Helicobacter pylori* (71). Furthermore, two case reports described patients bearing gastroparesis who benefited from the switching to softgel thyroxine to overcome the refractory hypothyroidism due to gastric motility impairment (72, 73)

The clinical efficacy of softgel formulation in a patient concomitantly treated with proton pump inhibitors has been described in a case-report (74). The better performance of softgel was confirmed by the indices of absorption, evaluated following an acute load with 600 mcg of thyroxine of the two formulations (74). Furthermore, the lesser impact of concomitant breakfast ingestion on softgel capsule preparation performance has been reported (75). To note, a study including patients with gastric disorders demonstrated that the switch from tablet to softgel levothyroxine causes a smaller number of dose adjustments, thus saving health costs (76).

The bioequivalence of the liquid thyroxine preparation to tablet thyroxine has been proven but, oving to the fact that the active ingredient is already dissolved, the time to reach systemic circulation is significantly shorter as compared to both tablet and softgel preparations (77). Some case series reported the usefulness of this formulation in small group of patients with active *H. pylori* infection (78) or bearing atrophic gastritis (79). The liquid T4 formulation has been proven helpful also in the case of concomitant treatment with proton pump inhibitors and several drugs with antacid action (80, 81). A further relevant issue is the effect of food co-ingestion on liquid thyroxine absorption: two papers agreed in defining this formulation less sensitive to the interfering action of food when compared to the traditional one (82, 83). Noticeably, a study on more than 50,000 thyroxine treated patients demonstrated a significant reduction in the number of serum TSH measurements after switching from tablet to liquid formulation (84). These results chiefly pertain to patients using drugs interfering with levothyroxine absorption (84). Liquid formulation has been also proposed in a case of sleeve gastrectomy (85). A recent meta-analysis on studies in which patients on tablet T4 showed suboptimal TSH values indicated that the switch to liquid T4 formulation, at the same daily dose, might help in reaching the target TSH levels (86). A further meta-analysis reported no significant differences in patients without malabsorption but claimed that liquid thyroxine is more efficient than tablet L-T4 in treated patients with malabsorption (87).

CONCLUSIONS

Endocrinologists and physicians should be aware of the role of the stomach on the subsequent intestinal absorption when treating patients with levothyroxine.

AUTHOR CONTRIBUTIONS

CV and MC conceived of and designed the study. SC and NB performed the literature search. All authors contributed to the article and approved the submitted version.

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REVIEW
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Levothyroxine Therapy in Thyrodectomized Patients

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Administration of the optimal dose of levothyroxine (LT4) is crucial to restore euthyroidism after total thyroidectomy. An insufficient or excessive dosage may result in hypothyroidism or thyrotoxicosis, either one associated with a number of symptoms/complications. Most literature regarding the LT4 dosage deals with the treatment of primary hypothyroidism, whereas a limited number of studies handle the issue of thyroxin replacement after total thyroidectomy. A literature review was performed focusing on all papers dealing with this topic within the last 15 years. Papers that reported a scheme to calculate the proper LT4 dose were collected and compared to set up a review exploring limits and drawbacks of LT4 replacement therapy in the wide population of patients who had undergone thyroidectomy. Most of the methods for monitoring and adjusting thyroid hormone replacement after thyroidectomy for benign disease use LT4 at an empirical dose of approximately 1.6 μg/kg, with subsequent changes according to thyroid function test results and assessments of the patient's symptoms. Approximately 75% of patients require a dose adjustment, suggesting that factors other than body weight play a role in the determination of the proper LT4 dose. Hence, several schemes are reported in the literature for the proper initial dose of LT4. An inadequate level of thyroid hormone levels in these patients can be due to several factors. The most common ones that lead to the necessity of LT4 dose adjustments include lack of compliance, changes in LT4 formulation, dosage errors, increased serum levels of T4-binding globulin, body mass changes, and dietary habits. Moreover, concomitant ingestion of calcium supplements, ferrous sulfate, proton-pump inhibitors, bile acid sequestrants, and sucralfate might influence LT4 absorption and/or metabolism. Furthermore, some gastrointestinal conditions and their treatments can contribute to suboptimal LT4 performance by altering gastric acidity and thereby reducing its bioavailability, particularly in the solid form. Beyond the classic tablet form, new formulations of LT4, such as a soft gel capsule and an oral solution, recently became available. The liquid formulation is supposed to overcome the food and beverages interference with absorption of LT4 tablets.

Keywords: thyroid, levothyroxine, thyroidectomy, liquid levothyroxine, levothyroxine dose

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INTRODUCTION

There is a wide consensus among different authors that a relevant percentage of patients taking levothyroxine (LT4) for hypothyroidism induced by different causes show a non-perfect compliance with therapy that necessitates several changes and adjustments during their treatment (1, 2). Inadequate dosage may result in hypothyroidism or hyperthyroidism, both involving serious sequelae at several different levels. Overtreatment causes hyperthyroidism and associated cardiac symptoms, weight loss, insomnia, and heat intolerance (3). On the other hand, overt and subclinical hypothyroidism have both been associated with unfavorable changes in several metabolic parameters, including lipid profile and glucose control, as well as with higher blood pressure and insulin resistance, all conditions that may amplify the cardiovascular disease risk in type 2 diabetes. Similar associations have also been reported for thyroid-stimulating hormone (TSH) levels in the upper part of the normal reference range (4, 5).

This review examined the literature involving hypothyroid patients who underwent a total or near-total thyroidectomy to understand the problems they generally encounter with their replacement therapy. For this purpose, the literature review focused on all papers dealing with this topic during the last 15 years. Only eight of these studies also contained a proposal to work out a scheme for the prediction of the LT4 requirement after thyroidectomy.

Common factors that can lead to LT4 dose adjustments include lack of compliance, changes in the LT4 formulation, dosage errors, increased serum levels of T4-binding globulin, body mass changes, and dietary habits (1, 6). Concomitant ingestion of calcium supplements, ferrous sulfate, proton-pump inhibitors, bile acid sequestrants, and sucralfate can also influence LT4 absorption and/or metabolism (6, 7).

LT4 is a medication with a narrow therapeutic index, and its absorption is dependent on gastric pH (1, 6). Indeed, acid production is reducted in patients with chronic gastritis or gastric atrophy, in those treated with proton-pump inhibitors, and in patients with *Helicobacter pylori* infection: all of these conditions have been related to increased thyroxine requirement (6).

Some gastrointestinal conditions and their treatments can contribute to suboptimal LT4 performance by altering gastric acidity and thereby reducing the bioavailability of LT4. Defects in absorption of thyroid hormones are reported in patients with previous gut surgery, celiac disease, lactose intolerance, autoimmune gastritis, or *Helicobacter pylori* infection (6, 8, 9).

Most of the debate in the past was focused on LT4 dosage and possibly on the timing of the administration. More recently, however, increasing attention has also been paid to the formulation of LT4. The liquid form in two presentations—a soft gel capsule and as an oral solution—recently became available for LT4 replacement therapy (10). Notably, a population-based study of 55,000 LT4 users reported a significant reduction in the number of TSH measurements after switching from the tablet to the liquid form, particularly in patients using drugs that potentially interfere with LT4 absorption (11). These papers addressing the liquid form report some promising results also in patients who have undergone thyroidectomy (12, 13).

Another important issue is the possible necessity of a suppressive thyroid hormone treatment in those patients who have undergone a total thyroidectomy for a differentiated thyroid cancer (DTC). This might imply a long-term treatment with LT4 to the extent that in these patients it is even more important to individualize the therapy to balance accurately its supposed benefits against the potential risk of adverse effects during follow-up. A proper selection then becomes of paramount importance (8). American Thyroid Association (ATA) guidelines help in determining the class of risk in patients, mainly represented by the presence of distant metastases, and the response to the initial treatment. On the other hand, advanced age, risk factors, and underlying comorbidities might play an important role against TSH suppression, and the latter should be avoided (14, 15). For these reasons and because of the low risk of recurrence and death in DTC, ATA recommends a graded algorithm in which the potential benefits of this therapy are carefully weighed against its cardiovascular and skeletal risks (14, 15).

LITERATURE REVIEW

A literature review focused on papers reporting LT4 treatment in patients after a total or near total thyroidectomy. Data were collected and scrutinized from the PubMed database using combinations of the following search terms: levothyroxine, dosing, thyroidectomy, differentiated thyroid cancer, and liquid levothyroxine. Additional studies were selected through reference lists of articles known to be relevant. We only considered articles that were published in the last 15 years and investigated LT4 treatment in adults (aged ≥18 years) after total, near-total, or completion thyroidectomy. Only articles written in English were included.

LT4 Dosing Schemes After Total Thyroidectomy

Most of literature regarding the LT4 dosage deals with the treatment of primary hypothyroidism, whereas only few studies handle the issue of thyroxine replacement after total thyroidectomy (16). As reported by Del Duca et al. (17) in a longitudinal study including 23 goitrous patients treated with LT4, the therapeutic dose of T4 after total thyroidectomy must be increased by one-third compared with the presurgical one. This additional amount of T4 may be the substrate for the peripheral deiodinase network to compensate the absence of T3 production from the gland (17).

Most of the methods for monitoring and adjusting thyroid hormone replacement after thyroidectomy for benign disease use LT4 at an empirical dose of approximately 1.6 μg/kg, with subsequent changes based on thyroid function test results and assessments of the patient's symptoms (2). Approximately 75% of patients require dose adjustments, suggesting that body weight is not the only factor involved in the determination of the proper LT4 dose (3). On the basis of our literature review, we singled out eight schemes proposed to calculate the proper dose of LT4 after thyroidectomy (**Table 1**). These schemes take into consideration a combination of the following parameters: body weight, age, body surface area (BSA),

TABLE 1 | Main proposed schemes for the prediction of LT4 requirement after total thyroidectomy.

Study	Type of study	Number of patients	Formula/nomogram
Olobuwale et al. (16)	Prospective	27	LT4 dose (μg/day) = - 100 if weight <53 kg - 125 if 53 ≤ weight ≤ 86 kg - 150 if 86 < weight ≤ 108 kg - 175 if weight >108 kg
Mistry et al. (2)	Prospective	100	LT4 dose (μg/day) = (0.943 × weight) + (–1.165 × age) + 125.8 (Simplified to = weight – age + 125)
Ojomo et al. (7)	Retrospective	122	LT4 dose (μg/day) = (–0.018 × BMI + 2.13) × weight
Jin et al. (18)	Retrospective	400	LT4 dose (μg/day) = 1.5 × weight
Di Donna et al. (19)	Prospective	31	LT4 dose (μg/day) = BMI ≤23 23–28 >28 Age ≤40 1.8 1.7 1.6 >40–55 1.7 1.6 1.5 >55 1.6. 1.5. 1.4
Elfenbein et al. (20)	Prospective	180	LT4 dose (μg/day) = Male Female BMI (kg/m^2) ≤ 21 2.1 1.8 22–26 1.9 1.7 27-32 1.7 1.6 33-40 1.5 1.4 >40 1.3 1.2
Zaborek et al. (21)	Retrospective	598	LT4 dose (μg/day) = e^x x = 2.02 + 0.01 (weight) – 0.0037 (age) – 0.098 (sex) – 0.01 (BMI) + 0.007 (preoperative TSH) + 0.108 (iron supplementation) – 0.014 (mineral supplementation) Note: patient sex: 1 for female, 0 for male; iron supplementation: 1 for supplementation, otherwise 0; mineral supplementation: 1 for supplementation, otherwise 0.
Al Dahiri et al. (22)	Retrospective	234	LT4 dose (μg/day) = - If BSA > 1.79 m^2 1.4 x weight - If BSA ≤ 1.79 m^2 1.7 x weight

iron supplementation, mineral supplementation, preoperative TSH concentration, sex, or body mass index (BMI). The heterogeneity of these schemes implies the contribution of several parameters to the LT4 dose calculation and raises the need for an accurate, simple, and widely shared formula.

In particular, Olobuwale et al. (16) and Jin et al. (18) developed two different weight-based schemes to calculate the proper LT4 dose in patients who underwent thyroidectomy. Nevertheless, when retrospectively applied by other authors, the rate of patients being reported to be euthyroid at the first postsurgery follow-up was amendable, ranging between 23 and 53.2% (19, 21). Furthermore, Jin et al. (18) included patients who had undergone total thyroidectomy or lobectomy, making their data not homogeneous.

Successively, other schemes were proposed. Mistry et al. (2) introduced age as a factor to be considered along with body weight to calculate the proper LT4 dose. They compared their formula to the empirical dose of 100 μg and to the only weight-based dose calculation (1.6 μg × kg), finding that 72, 59, and 40% of patients, respectively, achieved the target within 25 μg of their proper dose. Even this formula, when applied retrospectively, did not lead to better results.

A remarkable improvement was obtained when schemes using BMI were introduced. First, Ojomo et al. (7) proposed a formula that takes into consideration both BMI and actual body weight, with optimal results. This formula was applied retrospectively and compared with the other existing schemes, both by Di Donna et al. and Zaborek et al. and resulted as the most accurate method (19). Afterward, Di Donna et al. and Elfenbein et al. produced schemes that take into account age and sex categories, respectively, along with BMI (19, 20) Di Donna et al applied their scheme prospectively to a cohort of 31 patients, achieving euthyroid status at the first follow-up in 68% (19). On the other hand, when the formula proposed by Elfenbein et al. was retrospectively applied to a cohort of 180 patients, it predicted the eventual euthyroid dose of LT4 to within 20 μg for 61% of patients (20).

An important step forward was made by Zaborek et al. who developed a Poisson regression formula that takes into account seven factors: four of them were found in previous proposed schemes (actual body weight, BMI, age, sex), whereas the remaining three additional factors were preoperative TSH, vitamin-mineral supplementation, and iron supplementation (21). In this study of a retrospective cohort of 598 patients, their scheme outperformed the other previously proposed schemes, predicting 64.8% of the corrected doses at the first follow-up. To promote the use of Poisson regression to estimate the proper LT4 dose, the authors developed an easy-to-use web application that allows the physicians to insert the patient's parameters and automatically calculate the LT4 dose.

Finally, in 2019, Al Dhahiri et al. (22) performed a study to identify factors that would predict the LT4 dose after thyroidectomy. Their analysis showed BSA as an independent predictor of the LT4 dose. The authors developed two different and very complex formulas (one polynomial and one linear) for predicting the LT4 dose after thyroidectomy, with a rate of correct estimation of 65.8 and 51.3%, respectively. They also created a model that takes into consideration only BSA as a unique parameter, competent to predict 64.5% of the corrected dose. Nevertheless, due to the complexity of calculating the dose, finding a practical and clinically relevant prediction model is yet of limited efficiency.

Differentiated Thyroid Cancer

Thyroid hormone treatment plays a central role in the postoperative management of DTC. Nevertheless, long-term treatment with LT4 should be individualized and weighed against the potential risk of adverse effects, and patients who require suppressive therapy should be appropriately selected (8). Thus, before LT4 therapy is administered, it is of paramount importance to consider, along with the risk of persistent or recurrent disease and the response to the initial treatment, whether poor general health status and comorbidities (in

particular, bone and cardiac diseases) contraindicate TSH suppression (14). Furthermore, Jin et al. reported that TSH-suppression therapy after thyroidectomy due to DTC could lead to depression, short-term memory and attention impairment, and word selection anomia (18).

Given the evidence that aggressive TSH-suppressive therapy led to little or even no benefit in almost all patients who underwent total thyroidectomy for DTC, ATA guidelines recommended a scheme in which the potential advantages of this therapy are carefully balanced against its cardiovascular and skeletal collateral effects (7, 8). Especially in elderly patients, who have an increased risk of osteoporosis and atrial fibrillation, the TSH target should be carefully selected (23).

According to the most recent Italian Consensus on Diagnosis and Treatment of DTC, after the initial therapy, patients included in the ATA high-risk category should be maintained at TSH suppression below 0.1 mU/L, unless contraindicated by comorbidities or advanced age (shift the target to 0.1–0.5 mU/L). Patients included in the ATA intermediate-risk category should be maintained at TSH levels between 0.1 and 0.5 mU/L. Finally, patients included in the ATA low-risk category, with undetectable thyroglobulin, should maintain a TSH level between 0.5 and 2 mU/L, whereas the level decreases to 0.1–0.5 mU/L if the thyroglobulin is low. In case of comorbidities or advanced age, the low- and intermediate-risk categories should both maintain TSH levels between 0.5 and 2 mU/L (24).

Concerning the degree of suppression during follow-up, regardless the initial ATA class risk classification, patients with excellent response to therapy should maintain a TSH level between 0.5 and 2 mU/L, regardless of comorbidities and age. Furthermore, patients with biochemical incomplete or indeterminate response should maintain a TSH level between 0.1 and 0.5 mU/L, which increases to a level between 0.5 and 2 mU/L in case of comorbidities or advanced age. Finally, patients with a structural incomplete response should maintain a TSH level lower than 0.1 mU/L, unless there are comorbidities or advanced age, which would shift the target to 0.1–0.5 mU/L (24).

Further, Carhill et al. (25) in 2015 analyzed a registry of 4,941 patients with DTC who had undergone a total thyroidectomy or near-total thyroidectomy with a median follow-up of 6 years. They reported that moderate thyroid hormone suppressive therapy, with TSH maintained in subnormal to normal levels, was associated with an improvement of overall survival and disease-free survival across all stages of DTC and that aggressive thyroid hormone suppressive therapy (TSH maintained undetectable-subnormal) showed no additional survival benefit (25).

In a study of 148 consecutive patients who underwent total thyroidectomy for DTC, Ito et al. investigated the relationship between symptoms and serum TSH and FT3 levels (26). Symptoms reflecting thyroid function were documented and compared preoperatively and postoperatively after 12 months of LT4 therapy. The authors found that in patients with strongly suppressed TSH levels, significant changes in symptoms with a tendency toward thyrotoxicosis were reported. However, patients with normal TSH levels experienced changes in symptoms with a tendency toward hypothyroidism. Lastly, in patients with mildly suppressed TSH levels and FT3 levels superimposable to the preoperative values, all symptoms remained equivalent to their preoperative levels. On the basis of their study, they claimed that patients with mildly suppressed TSH levels were closer to the euthyroid status and suggested that these finding were directly applicable to the management of patients who underwent total thyroidectomy for DTC or benign thyroid disease (26).

Liquid and Soft Gel Formulations

Beyond the classic tablet, new formulations of thyroxine can now be prescribed as a soft gel capsule and oral solution, which have been shown to overcome the food and beverages interference with absorption of LT4 tablets. In addition, the liquid formulation was of particular interest in case of malabsorption resulting from atrophic gastritis, proton-pump inhibitors, or after bariatric surgery. Malabsorption induced by lactose intolerance or drug interference can also be avoided (12). In particular, Benvenga et al. (27) addressed this topic in a study of 19 hypothyroid patients with tablet LT4 malabsorption caused by calcium and/or iron supplements and who were switched to liquid LT4 at the same dose. The authors reported that the TSH level was lower with the liquid LT4 compared with tablet LT4 form, concluding that liquid LT4 is resistant to the sequestration by calcium or iron. Moreover, the high rate of TSH normalization at the first check should avoid frequent adjustments in LT4 doses, with consequent financial savings.

The liquid LT4 also seems to be more active than tablets in the control of TSH even in hypothyroid patients without malabsorption, drug interference, or gastric disorders, leading to the hypothesis that absorption of liquid LT4 is also higher in this cohort (12).

Our literature review resulted in eight papers dealing with the administration of a liquid or soft gel capsule formulation in patients who underwent total thyroidectomy. These studies are summarized in **Table 2**.

Fallahi et al. (12) in 2018 conducted a prospective study of 105 patients who underwent total thyroidectomy for thyroid cancer, 52 of whom were treated with the liquid LT4 formulation and 53 with LT4 tablets at the same dosage (1.5 μg/kg/day). TSH levels were significantly lower in patients treated with liquid LT4, suggesting a higher absorption with this formulation (12). In particular, the rate of patients in the hypothyroid range was significantly higher in the solid form LT4 group (13.5%) compared with the liquid LT4 group (1.8%). The authors underlined the effectiveness of liquid LT4 over the tablet formulation to achieve the proper TSH levels in patients treated with total thyroidectomy for thyroid cancer.

Similarly, Cappelli et al. (13) performed a prospective randomized study of 102 patients who underwent total thyroidectomy and radioactive iodine therapy for DTC and were classified as low risk according to the 2009 ATA guidelines. The use of tablets, compared with treatment with the LT4 liquid formulation, resulted in a higher number of DTC patients with TSH values out of range for the ATA risk score (15.7 *vs.* 3.9%)

TABLE 2 | Prospective studies dealing with liquid or soft gel formulation of LT4 administered post total thyroidectomy.

Study	Number of patients	Treatment groups	Main findings
Pirola et al. (28)	20	Liquid *vs*. tablet LT4 in patients with enteral feeding tube	- Liquid LT4 can be administered immediately without the need for an empty stomach. This formulation is more easily managed by nurses
Giusti et al. (29)	59	Liquid *vs*. tablet LT4 in patients with DTC	- Subjective complaints were significantly lower on the liquid (28%) than on the tablet (43%) L-T4 formulation - 73% requested to remain on the liquid formulation
Cappelli et al. (30)	60	Liquid *vs*. soft gel LT4 during breakfast	- Both formulations can be administered during breakfast - FT3 (2.5 *vs*. 2.7 pg/mL) and FT4 (9.9 *vs*. 10.6 pg/mL) levels during treatment with the soft gel capsule were significantly lower than those at enrollment with the liquid LT4 formulation
Lombardi et al. (31)	166	Liquid *vs*. tablet LT4	- Liquid LT4 could be more effective in improving mood states and self-perception of well-being
Cappelli et al. (13)	102	Liquid *vs*. tablet LT4 in patients with DTC	- 14.2% of patients on tablets and 3.9% of patients on liquid formulation showed TSH levels > 0.5 mIU/L
Di Donna et al. (32)	103	Soft gel *vs* tablet LT4	- LT4 requirement is not significantly different, but TSH is significantly lower with the use of the soft gel capsule, 1.3 ± 0.9 *vs*. 1.8 ± 1.2, respectively
Fallahi et al. (12)	105	Liquid *vs*. tablet LT4 in patients with DTC	- The prevalence of patients in the hypothyroid range was significantly higher in the LT4 tablet group (13.5%) *vs*. the liquid LT4 group (1.8%)
Peirce et al. (33)	3	Liquid *vs*. tablet LT4 in patients with severe hypothyroidism after total thyroidectomy	All patients (100%) were restored to euthyroidism after switching from LT4 tablets to LT4 liquid form

during 24 months of follow-up. Moreover, no body weight changes were observed among the whole population enrolled.

A study by Peirce et al. (33) in 2018 of patients who underwent total thyroidectomy with severe hypothyroidism reported that euthyroidism was progressively restored after sublingual administration of liquid LT4, making this formulation a valid alternative method for acute treatment of severe hypothyroidism.

Further, Giusti et al. (29) conducted a study of 59 patients with cured DTC who were switched from the tablet to the liquid formulation of LT4 and found no change in TSH, thyroid hormones, and thyroglobulin levels during the study. Although significantly more patients found the tablet form more agreeable, subjective symptoms had decreased significantly at the end of the study, and 73% of patients requested to remain on the liquid formulation (29). The authors concluded that liquid LT4 could be considered as a valid alternative formulation in patients after thyroidectomy for DTC and that the initial dislike by the patients was overcome by a significant decrease in subjective symptoms.

Lombardi et al. (31) performed a prospective randomized study in 2016 of 155 patients who had undergone total thyroidectomy and evaluated the patients' mood state and their self-perception of mental well-being during a follow-up period of 2 months. Their study found that the liquid formulation resulted in a significantly greater efficacy in ameliorating these parameters.

Other notable aspects were evaluated by Pirola et al. (28). They recruited 20 patients who underwent laryngectomy along with thyroidectomy and who were randomized in two groups, one was treated with LT4 tablets, and one was treated with LT4 liquid formulation. The authors concluded that the liquid form of LT4 can be administered directly through the nasogastric tube without the need for an empty stomach and is more easily managed by a nurse.

In addition to the liquid LT4, another new formulation of LT4 is represented by the soft gel capsule. In 2014, Di Donna et al. (32) studied 103 patients who had undergone total thyroidectomy for benign diseases. Once a stable normal TSH value was achieved using the tablet formulation, the patients were switched to treatment with the soft gel capsule at the same previous dose. The LT4 dose required for achieving normal TSH values did not differ between tablets and the soft gel capsule formulation. A statistically significant decrease of approximately 28% in the mean TSH level was documented with the use of the soft gel capsule formulation, which may represent an important advantage considering the possible association between elevated FT4 levels, even in euthyroid patients, and cardiovascular disease.

In a recent study, soft gel capsule and liquid formulations given during breakfast were compared for their effects on thyroid hormone profile. Although both formulations can be taken during breakfast, the liquid one should be preferred for patients in whom even small changes of thyroid hormones levels must be avoided (30).

CONCLUSION

Despite a remarkable commitment by researchers to find a therapeutic scheme able to predict the exact dose of LT4 to be given to patients after a total thyroidectomy, the attempt to reach the precise dosage failed to reach the target in the totality of the cases. It is reasonable to conclude that because most of the schemes show a considerable complexity but do not offer significant advantages in the percentage of patients reaching the expected results, the search for a fully predictive model seems to be an exercise of futility. Nonetheless, these schemes are of great utility to start the replacement therapy approaching the best dosage, but keeping in mind that changes during follow-up can be necessary according to the TSH values that are to be reached in every case.

Finally, data from the review seem to demonstrate that a significant role will be played by the liquid formulation of LT4, mainly for two reasons: first, because its absorption is easier and quicker than the tablet format, and second, it facilitates a more rapid control of TSH in patients with any kind of malabsorption and probably also in patients without this problem.

AUTHOR CONTRIBUTIONS

LR wrote the manuscript with the support of PM and collected data for the literature review. Moreover, LR reviewed the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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The Recovery of Thyroid Function in Low-Risk Papillary Thyroid Cancer After Lobectomy: A 3-Year Follow-Up Study

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Purpose: Management strategies after lobectomy for low-risk papillary thyroid carcinoma (PTC) are controversial. This study aimed to identify the proportion of patients among low-risk PTC patients who do not require hormone replacement therapy and to evaluate the risk factors for postoperative hypothyroidism after lobectomy.

Patients and Methods: The records of 190 PTC patients who underwent thyroid lobectomy from January 2017 to December 2018 were retrospectively reviewed. Clinicopathological characteristics and follow-up data were collected. Univariate and multivariate analyses were performed to identify the risk factors associated with postoperative hypothyroidism and the recovery of thyroid function.

Results: In summary, 74.21% of patients (141/190) had normal thyroid function without levothyroxine supplementation, while 40.53% (77/190) developed temporary or permanent hypothyroidism. Multivariate analysis indicated that higher preoperative thyroid-stimulating hormone (TSH) levels (>2.62 mIU/L), Hashimoto's thyroiditis (HT), and right lobectomy were associated with hypothyroidism (all $P<0.05$). The Area Under Curve (AUC) by logistic analysis was 0.829. Twenty-eight (28/77, 36.4%) patients recovered to the euthyroid state in the first year after surgery, and this recovery was significantly associated with preoperative TSH level. Forty-nine (49/77, 63.6%) patients developed persistent hypothyroidism. The thyroid function of most patients (11/28, 39.3%) recovered in the third month after surgery.

Conclusion: Patients with a lower level of preoperative TSH, with left lobectomy and without Hashimoto's thyroiditis had a higher chance of normal thyroid function within the first year after lobectomy. The recovery of thyroid function was associated with the level of preoperative TSH.

Keywords: papillary thyroid cancer, hypothyroidism, thyroidectomy, thyrotropin, lobectomy

INTRODUCTION

Thyroid cancer is the sixth most common malignancy in women (1), and its incidence has rapidly increased in recent years. Lobectomy is recommended as a standard initial treatment for low-risk papillary thyroid carcinoma (PTC) in both the National Comprehensive Cancer Network (NCCN) (2) and European Society for Medical Oncology (ESMO) guidelines (3). The American Thyroid Association (ATA) guidelines (4) also provide a strong recommendation for lobectomy in patients with thyroid cancer <1 cm. Even experienced surgeons cannot avoid complications caused by expansion of the operative extent in total thyroidectomy. Furthermore, lobectomy patients can benefit from fewer complications (5), such as hypocalcaemia or injury of the recurrent laryngeal nerve (6). Moreover, the overall survival (7) and disease-free survival (DFS) (8) rates are similar between patients who undergo lobectomy and total thyroidectomy, as reported by previous studies. However, the management of postoperative thyroid function remains controversial among patients. Most studies have shown that 9%–64.2% of patients develop hypothyroidism after lobectomy (9–11). This controversy comes from differences in the definition of hypothyroidism, patient follow-up time, and the duration of thyroid hormone replacement therapy (12).

Due to the widespread use of thyroid hormone therapy in the clinic, patients begin to take thyroid hormone in the early postoperative period. However, monitoring thyroid function in patients interferes with thyroid hormone therapy. Moreover, thyroid hormone therapy has many side effects in patients with long-term hyperthyroidism/subclinical hyperthyroidism as a result of long-term overdose and failure to provide regular monitoring. The incidence of kidney, pancreatic, ovarian, and breast cancers was found to increase with long-term iatrogenic hyperthyroidism according to a large-sample epidemiological study in Norway (13). A cohort study (14) also described the association between thyroid-stimulating hormone (TSH) levels and risk of cardiovascular disease.

The purpose of this study was to determine the proportion of patients who do not need hormone replacement therapy and to determine its predictors of this outcome by following patient thyroid function. The relative factors and average time of recovery to the euthyroid state were analyzed to determine the surgical strategy and management of postoperative thyroid function in patients with low-risk thyroid carcinoma.

MATERIALS AND METHODS

Patients and Study Design

A total of 253 patients who underwent unilateral lobectomy due to PTC at the Department of Endocrine and Breast Surgery of the First Affiliated Hospital of Chongqing Medical University from January 2017 to December 2018 were enrolled in this retrospective analysis. Patients with hyperfunctioning thyroid adenoma (n=5), other types of carcinoma (n=5), lymphatic positivity (n=11), hypothyroidism before operation (n=14) or a lack of follow-up data (n=28) were excluded. Based on these criteria, 190 patients with PTC were included. Consent was obtained from each patient after full explanation of the purpose and nature of all procedures. The study was approved by the Medical Ethics Committee of The First Affiliated Hospital of Chongqing Medical University (2020-219).

Clinicopathological Variables

Age, sex, tumor size (maximal diameter), tumor location (upper/middle/lower pole), body mass index (BMI), resection of the left/right lobe, Hashimoto's thyroiditis (HT), preoperative TSH, and postoperative thyroid function at every follow-up visit were recorded as the patient clinicopathological variables. The diagnoses of PTC and HT were confirmed by pathological examination. Patients with normal preoperative TSH levels were divided into two groups (euthyroid group vs. hypothyroidism group) based on the levels of postoperative TSH, serum free thyroxine (fT4), and total serum thyroxine (TT4). Within the hypothyroidism group, patients were enrolled in the recovery group if their thyroid function returned to a normal level without hormone intake. Otherwise, they were enrolled in the group of patients who did not recover to normal thyroid function (non-recovery), which included patients who received thyroid replacement therapy and could not stop hormone dependence (n=49) (**Figure 1**).

Surgical and Follow-Up Procedures

All patients were diagnosed *via* fine-needle aspiration biopsy (FNAB) before surgery. Lymph node status was estimated by two experienced ultrasound doctors. Thyroid function and thyroid autoantibodies were tested before operation. Patient treatment and risk factor assessments were made in accordance with both the ATA and Chinese guidelines, and the scope of surgery was at least lobectomy on the affected side and central lymph node dissection of the affected side. Low-collar incision minimally invasive lobectomy with unilateral central compartment lymph node dissection (LND) was performed in those patients. Intraoperative frozen biopsy was routinely performed in each patient to determine the extent of surgery. The contralateral thyroid lobe was retained only if frozen biopsy confirmed no lymph node involvement. In this way, the risk of recurrence in the contralateral thyroid lobe was minimized. Therefore, we did not immediately administer hormone therapy to these patients. Patients were followed in the first month, every three months during the first postoperative year, and then every six months during the second and third years. Thyroid function and related symptoms were carefully evaluated. Neck ultrasonography was performed for suspected recurrence and metastasis at each follow-up visit. During our follow-up period (20-36 months), no patient showed definite cervical lymph node or residual thyroid lobe recurrence. Patients with TSH levels >10 mIU/L (significantly higher risk of cardiovascular mortality and morbidity) or TSH levels >5.9 mIU/L with serious intolerable hypothyroid signs, such as severe asthenia, myxoedema or heart failure, were given L-thyroxine (15). The dosage of thyroid used for replacement was 50–150 μg/day, and the dosage was adjusted according to the patient's thyroid function laboratory tests. We would reduce the levothyroxine dose by 25 μg at each follow-up time. When patients fell into a state of clinical hypothyroidism,

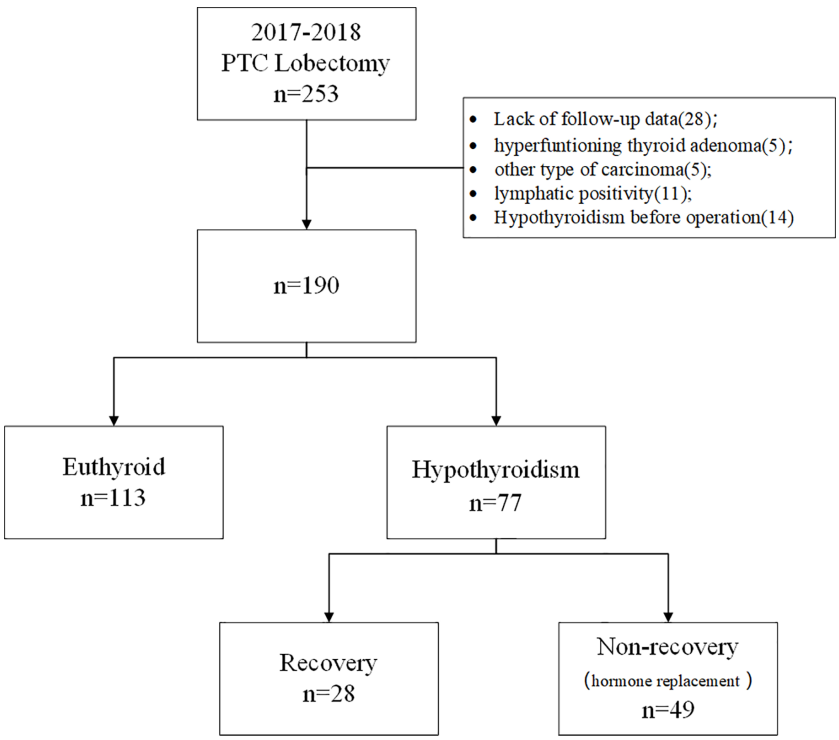

FIGURE 1 | Study flowchart.

or subclinical hypothyroidism with hypothyroid symptoms, the levothyroxine dose would be increased appropriately. When patients showed subclinical hypothyroidism without hypothyroid symptoms, they were transiently observed without immediate hormone therapy until the other follow-up examination. The dose would be increased if their TSH levels rose continually. Otherwise, thyroid function was continuously monitored without hormone replacement therapy.

Laboratory Measurements

All blood samples were tested by two experienced laboratory doctors. Thyroid function laboratory tests included tests of free triiodothyronine (fT3), total triiodothyronine (TT3), free thyroxine (fT4), total thyroxine (TT4), TSH, thyroglobulin (TG), and anti-thyroglobulin antibodies (TGAb) levels. All parameters were tested at each follow-up visit. The normal serum reference ranges for TSH, fT4, TT4, Tg, TgAb, and thyroperoxidase autoantibody (TPO) from our Clinical Laboratory Department were 0.56–5.91 mIU/L, 0.59–1.25 ng/dl, 5.44–11.85 μg/dl, 5–50 μg/L, 0–4 mIU/L, and 0–9 mIU/L, respectively. Hypothyroidism included subclinical hypothyroidism (15), which was defined as abnormal TSH values and FT4 and fT4 values within the reference range (TSH>5.91 mIU/L with normal fT4 and TT4 levels in our hospital), and clinical hypothyroidism, which was defined as abnormal TSH values with decreased fT4 or TT4 (TSH>5.91 mIU/L with fT4<0.59 ng/dl or TT4 <5.44 μg/dl in our hospital). No patient was pregnant during the perioperative period or the whole follow-up period.

Statistical Analyses

Univariate and multivariate data were analyzed using SPSS version 23.0 (SPSS Inc., Chicago, IL, United States). Student's t-test was used to examine continuous variables, which were described as the means with standard deviations. The x^2 test was performed to analyze the categorical variables. Receiver operating characteristic (ROC) curve analysis was performed to analyze the cut-off value for the predictive ability of preoperative TSH for postoperative hypothyroidism. Logistic regression analysis was used to analyze multivariate variations between the euthyroid group and hypothyroidism group and between the recovery group and the non-recovery group. Survival curves describing thyroid function recovery during follow-up were analyzed by Kaplan-Meier analysis. A two-tailed P-value below 0.05 was used to indicate statistical significance. Both the thyroid function curves for the different subgroups and the histograms were prepared with GraphPad Prism 8.0 (GraphPad Software Inc., San Diego, CA, USA).

RESULTS

Clinicopathological Patient Characteristics

Among the total of 190 patients, 113 (59.47%) patients remained in the euthyroid state during the whole follow-up period after operation, while 77 (40.53%) developed temporary or permanent hypothyroidism. The sex characteristics of the 190 patients (140

TABLE 1 | Univariate analysis of factors associated with euthyroid group and hypothyroid group in 190 patients with euthyroid before operation.

	Totaln=190	Euthyroid group	Hypothyroid group	P-value
		113	77	
Ages, years	40.4 ± 10.4	40.2 ± 9.9	40.9 ± 11.2	0.777
<55	175 (92.1%)	105 (92.9%)	70 (90.9%)	0.614
≥55	15 (7.9%)	8 (7.1%)	7 (9.1%)	
Size of tumor, cm	0.8 ± 0.6	0.8 ± 0.7	0.8 ± 0.5	0.992
≤1	158 (83.2%)	96 (85.0%)	62 (80.5%)	0.422
>1	32 (16.8%)	17 (15.0%)	15 (19.5%)	
Sex				0.077
Female	140 (73.7%)	78 (69.0%)	62 (80.5%)	
Male	50 (26.3%)	35 (31.0%)	15 (19.5%)	
Resection of Left/Right				0.005
Left	80 (42.1%)	57 (50.4%)	23 (29.9%)	
Right	110 (57.9%)	56 (49.6%)	54 (70.1%)	
Location				0.835
upper	61 (32.1%)	38 (33.6%)	23 (29.9%)	
middle	82 (43.2%)	47 (41.6%)	35 (45.5%)	
lower	47 (24.7%)	28 (24.8%)	19 (24.7%)	
BMI	22.9 ± 3.2	22.9 ± 3.2	22.7 ± 2.9	0.870
TSH, mIU/L	2.4 (0.7–5.7)	1.9 (0.7–5.0)	3.4 (0.8–5.7)	<0.001
TPO, mIU/L	0.8 (0.0–971.0)	0.8 (0.0–971.0)	0.8 (0.1–880.0)	0.851
TgAb, mIU/L	0.1 (0.0–877.0)	0.1 (0.0–243.0)	0.2 (0.0–877.0)	0.045
Tg, μg/L	7.0 (0.2–464.0)	6.4 (0.2–464.0)	8.2 (0.2–88.0)	0.107
HT				
NO	178 (93.7%)	111 (98.2%)	67 (87.0%)	0.002
YES	12 (6.3%)	2 (1.8%)	10 (13.0%)	

BMI, Body Mass Index; TSH, thyroid-stimulating hormone; TPO, thyroperoxidase autoantibody; TgAb, anti-thyroglobulin; Tg, thyroglobulin; HT, Hashimoto's thyroiditis.

(73.7%) females and 50 (26.3%) males) are presented in **Table 1**. The average age at diagnosis was 40.4 ± 10.4 years, the average tumor size was 0.8 ± 0.6 mm, and the average BMI was 22.9 ± 3.2. The preoperative TSH, TPO, TgAb, and Tg levels were 2.4 (0.7–5.7) mIU/L, 0.8 (0.0–971.0) mIU/L, 0.1 (0.0–877.0) mIU/L, and 7.0 (0.2–464.0) μg/L, respectively. By univariate analysis, there was no significant difference in mean age, tumor size, sex, tumor location, BMI, TPO, or Tg between the two groups. More right lobectomy patients were hypothyroid (70.1% vs. 49.6%), and this difference was significant (P=0.005). High levels of preoperative TSH, high levels of TgAb, and HT were significant factors for postoperative hypothyroidism (P< 0.05 for all comparisons).

The optimum cut-off value of preoperative TSH, as analyzed by the ROC curve, was 2.62 mIU/L, with a sensitivity of 0.832 and specificity of 0.701. Multivariate analysis (**Table 2**) indicated that a higher preoperative TSH level (>2.62 mIU/L) was associated with hypothyroidism (OR = 12.567, 95% CI = 6.009 to 26.285; P<0.001). HT was the second independent risk factor, with an OR of 9.293, followed by right lobectomy. TgAb was not associated with the development of postoperative hypothyroidism. **Figure 2** shows the ROC curve from the logistic analysis, indicating an AUC of 0.829 (95% CI 0.735 to 0.862).

TABLE 2 | Multivariate logistic regression for predictive factors in relation to postoperative hypothyroidism in 190 patients with euthyroid before operation.

	β (SE)	P-value	OR	95% CI	
				Lower	Upper
TSH>2.62 mIU/L	2.531	0.001	12.567	6.009	26.285
preTgAb(+)	0.285	0.473	1.330	0.610	2.897
HT(+)	2.229	0.014	9.293	1.561	55.326
Right-lobectomy	0.877	0.021	2.404	1.139	5.077

TSH, thyroid-stimulating hormone; TgAb, anti-thyroglobulin; CI, confidence interval; OR, odds ratio.

Development of Hypothyroidism

In the hypothyroidism group, 28 (36.36%) patients recovered to the euthyroid state. Forty-nine (63.64%) patients, who ultimately took hormone replacement therapy, developed hypothyroidism and did not recover during the follow-up period. **Table 3** shows that there was no significant difference in age, tumor size, sex, tumor location, or preoperative BMI, TPO, TgAb, Tg, or HT. Only a higher preoperative TSH level significantly associated with non-recovery hypothyroidism (P=0.014), and this significant difference was also found by multivariate analysis.

We evaluated the postoperative changes in TSH in the different groups during the follow-up period (**Figure 3**). During the follow-up period, both the euthyroid group and recovery group maintained a relatively stable TSH level similar to their preoperative TSH level. The hypothyroid group showed a sharp fluctuation in TSH level due to the supplement therapy. There were no significant correlations between the recovery group and the euthyroid group according to Pearson correlation analysis (P=0.33). **Figure 4** shows the proportion of the two groups with thyroid function recovery and supplement therapy at each visit. The thyroid function of 11 (39.29%)

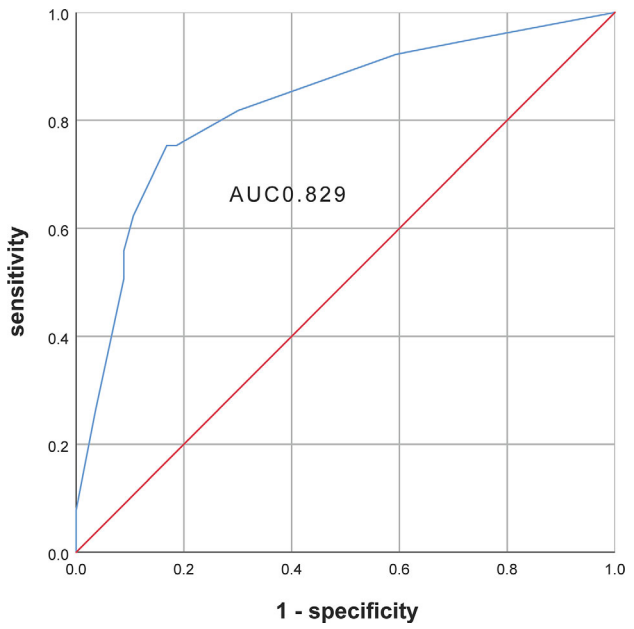

FIGURE 2 | The receiver operating characteristic (ROC) curve of multivariate analysis.

TABLE 3 | Univariate analysis between recovery group and non-recovery group.

	recovery group	non-recovery group	P-value
	28	49	
Ages, years	40.1 ± 11.9	41.3 ± 10.9	0.302
<55	25 (89.3%)	45 (91.8%)	0.708
≥55	3 (10.7%)	4 (8.2%)	
Size, cm	0.9 ± 0.5	0.8 ± 0.5	0.582
Sex			0.128
Female	20 (71.4%)	42 (85.7%)	
Male	8 (28.6%)	7 (14.3%)	
Resection of Left/Right			0.082
Left	5 (17.9%)	18 (36.7%)	
Right	23 (82.1%)	31 (63.3%)	
Location			0.511
upper	10 (35.7%)	13 (26.5%)	
middle	13 (46.4%)	22 (44.9%)	
lower	5 (17.9%)	14 (28.6%)	
BMI	23.0 ± 2.6	22.5 ± 3.1	0.275
TSH, mIU/L	2.5 (1.4–5.1)	3.5 (0.8–5.7)	0.014
TPO, mIU/L	1.4 (0.1–552.0)	0.8 (0.1–880.0)	0.212
TgAb, mIU/L	0.1 (0.1–380.0)	0.2 (0.0–877.0)	0.199
Tg, μg/L	9.5 (0.6–88.0)	8.0 (0.2–36.7)	0.206
HT			
YES	24 (85.7%)	43 (87.8%)	0.653
NO	4 (14.3%)	6 (12.2%)	

BMI, Body Mass Index; TSH, thyroid-stimulating hormone; TPO, thyroperoxidase autoantibody; TgAb, anti-thyroglobulin; Tg, thyroglobulin; HT, Hashimoto's thyroiditis.

patients had recovered in the third month, followed by 10 (35.71%) in the 6th month and 7(25.00%)in the 9th month. Moreover, no patient recovered in the last month. No patients from the recovery group developed hypothyroidism again.

DISCUSSION

Many studies have attempted to determine the proportion of patients with hypothyroidism after thyroid lobectomy. In a 35.7-month follow-up study reported by Jin Seong Cho et al. (16), 21.1% of patients developed hypothyroidism after lobectomy. Suyeon Park et al. (11) reported that 35% of patients with hypothyroidism recovered. Amanda Johner et al. (17) reported that 69.2% of patients recovered. In our study, among patients who had hypothyroidism after lobectomy, 38 (28/77, 36.36%) patients spontaneously recovered to the euthyroid state. Above all, 141 (141/190, 74.21%) patients were in the euthyroid state at 24–36 months after follow-up, and these patients were more likely than the other patients to avoid hormone replacement. Further follow-up observational studies are ongoing.

TSH is the main stimulator of thyroid tissue growth and secretor of thyroxine. No guidelines (3, 4) providing a clear recommendation for the follow-up time of postoperative thyroid function are available. Many institutions provide hormone therapy to patients immediately after surgery, which may not be helpful for the recovery of thyroid function (18). In this study, the third month was the peak time of thyroid function recovery. We believe that the recovery of thyroid function might occur mainly in the first year after lobectomy because no patients recovered in the 12th month of follow-up. This is in line with previous studies (19, 20). Lower preoperative TSH levels were associated with thyroid function recovery by univariate analysis. The ability to recovery might be related to lower TSH levels and the degree of lymphocytic infiltration (21) according to previous studies.

TSH suppression therapy for PTC with a low risk of recurrence is controversial (22). A score-matched cohort study reported by Suyeon Park et al. (23) showed no significant difference in DFS between the thyrotropin suppression group and no suppressive group (P=0.57). The ATA guidelines (4) suggest that low-risk patients with TSH < 2 mIU/L should avoid TSH suppression therapy. In addition, considering the excellent prognosis of PTC, the side effects of long-term iatrogenic hyperthyroidism should be considered. In 2013, a prospective study (24) described the association between TSH levels and the incidence rate of cardiovascular diseases. With the inclusion of 524 patients in the experimental group and 1,572 patients in the control group, for each 10-fold reduction in TSH level, the risk of cardiovascular disease mortality increased 3.1-fold. Bone loss and fracture risk were also associated with TSH suppressive therapy, especially in women (25). Therefore, the potential clinical benefits and side effects of TSH suppression need to be balanced. In our follow-up period, no recurrence occurred in those patients, indicating that TSH suppression is not required for low-risk PTC patients. We selected patients with negative pathologic lymph nodes (pN0) shown through central lymph node intraoperative frozen biopsy to reduce the potential risk of recurrence and metastasis with preservation of the contralateral thyroid lobe. Since TSH suppression therapy is not routinely given, unilateral lobectomy could maximize the benefit to patients.

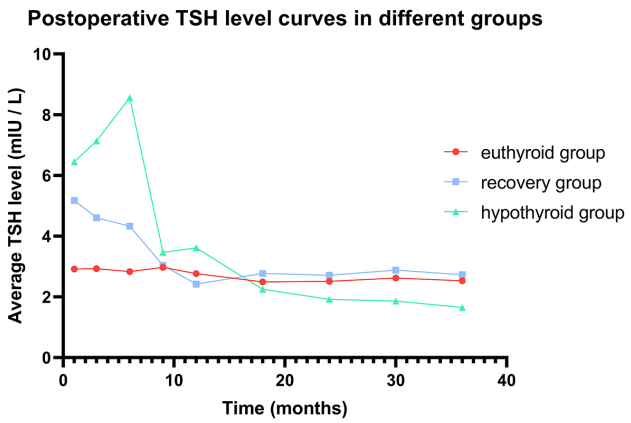

FIGURE 3 | Postoperative TSH level curves in different groups.

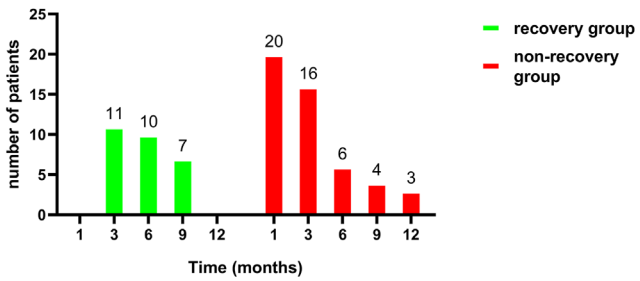

FIGURE 4 | Comparison of distributions between recovery (n=28) and non-recovery group (n=49) per visit month.

The association between postoperative hypothyroidism and preoperative TSH has been reported by many researchers (9, 19, 26). Jin Seong Cho et al. (16) found that the cut-off value for the preoperative TSH level in predicting postoperative hypothyroidism was 2.0 mIU/L. High preoperative TSH levels had an OR of 2.82 in predicting postoperative hypothyroidism in a cohort study (11). In our study, a high preoperative TSH level was the most independent factor of postoperative hypothyroidism (OR = 12.567, 95% CI = 6.009–26.285; P<0.001). In addition, a low preoperative TSH level was significantly associated with the recovery of thyroid function. Preoperative TSH levels can reflect patients' thyroid function and thyroid hormone storage. Patients with a high TSH level may have potential thyroid functional defects, thus preventing compensation by the residual thyroid after lobectomy.

Histological HT, the most common autoimmune disease (27), was the second predictor of postoperative hypothyroidism. Peng Ng et al. (28) reported that HT was the only independent risk factor in a retrospective review of 901 patients. The presence of thyroid antibodies was found to be a significant factor by univariate analysis but did not maintain independence as a factor for postoperative hypothyroidism by multivariate analysis. Thyroid antibodies might be associated with the disease mechanism and progression of HT. We speculate that when HT is tested at only the serological level, which means the disease may be mild and that thyroid function can still be compensated after the operation, hypothyroidism may occur later. When thyroiditis is detected by histology, which indicates later disease progression and the likely involvement of the contralateral residual thyroid, hypothyroidism may occur in the early postoperative period. For both serologic and pathological thyroiditis, hypothyroidism may inevitably occur after operation, and the benefit of lobectomy will be decreased. Furthermore, although still controversial, some articles suggest that HT is associated with the risk of developing thyroid cancer (29, 30). Therefore, we suggest total thyroidectomy for patients with HT.

Interestingly, we found that right-side lobectomy was an independent factor associated with postoperative hypothyroidism (OR 2.404; 95% CI 1.139–5.077; P=0.021), which is consistent with the present research (11). Some studies (31, 32) have considered the difference in size of the left and right lobes of the thyroid gland. The right thyroid lobe is usually larger in volume than the left. This asymmetry in thyroid size might result from differences in handedness. This asymmetry led to a significant risk for hypothyroidism when the residual thyroid tissue was small, as demonstrated by other reports (33). However, there may be some differences in blood supply and endocrine function between the left and right lobes of the thyroid gland. A large-sample study of 299,908 patients from Japan (34) showed that right lobe thyroid hemiagenesis was more common than left lobe thyroid hemiagenesis, a finding that requires further research regarding the embryology and physiology of the thyroid lobes.

There were several limitations in this study. First, we did not strictly restrict the diet of the study cohort (such as iodine intake), which may have had an impact on the laboratory test results. Second, considering the excellent prognosis of PTC, further research is underway with a longer follow-up time to verify the recovery time of thyroid function, recurrence rate, DFS, and overall survival. Third, unfortunately, our data did not include preoperative or postoperative residual thyroid volume. However, this was a unique study of low-risk PTC patients after unilateral lobectomy performed to identify the proportion of patients who benefited from lobectomy when interference from hormone supplementation was excluded.

In conclusion, our study indicated that 40.53% of PTC patients developed temporary or permanent hypothyroidism. Overall, 74.21% of patients were in the euthyroid state and likely to avoid hormone replacement. Postoperative hypothyroidism was independently associated with a higher level of preoperative TSH, HT, and right lobe lobectomy. TSH level were found to be related to the recovery of hypothyroidism. We suggest that low-risk patients be followed for at least one year to develop an individual thyroid function management strategy. Patients with lower preoperative TSH levels, without Hashimoto's thyroiditis, and with left lobe lobectomy might benefit more from lobectomy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethics Committee of The First Affiliated Hospital of Chongqing Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

The first author of this manuscript is YD. YD, DH, and XS designed this research. YC and DH collected the data and performed the statistical analyses. YD and XS reviewed the results, interpreted the data, and wrote the manuscript. YD, YC, and DH discussed and edited the paper. All authors contributed to the article and approved the submitted version.

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MINI REVIEW
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L-T4 Therapy in Enteric Malabsorptive Disorders

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Levothyroxine (L-T4) absorption can be impaired by various causes: a) L-T4 ingestion during breakfast, or with food; b) conditions of reduced gastric acidity; c) intestinal procedures and diseases such as bariatric surgery, lactose intolerance (LI), celiac disease (CD), inflammatory bowel disease; d) drugs that alter L-T4 absorption, increasing the gastric pH, or preventing the dissolution of tablets. The development of new oral formulations, i.e. the liquid preparation and the soft gel capsule, represents the most recent advance regarding L-T4 therapy. Treating hypothyroidism with L-T4 tablets can lead to an improper control of thyroid-stimulating hormone (TSH) in ~10%–15% of patients. The improperly elevated TSH is usually managed by increasing the L-T4 daily dose, and revaluating TSH upon 2-6 months. The increase of the L-T4 dosage may cause iatrogenic hyperthyroidism, especially when the underlying disorders are cured. Liquid L-T4 can be administered in patients unable to swallow capsules or tablets, and this is one of its major benefits. Liquid L-T4 can: 1- overcome food and beverages interference; 2- bypass the malabsorption associated with an increased gastric pH; 3- circumvent the issue of malabsorption in patients who underwent bariatric surgery; 4-maintain TSH values under control better than L-T4 tablets in hypothyroid patients with typical or atypical CD, or in patients with LI. Few clinical studies evaluated soft gel L-T4 with encouraging findings in patients with gastric- or coffee-related malabsorption, or hypothyroid patients without malabsorption. Additional research is necessary to investigate liquid L-T4, or soft gel capsule, in other conditions of altered L-T4 absorption.

Keywords: levothyroxine, hypothyroidism, enteric malabsorptive disorders, food interference, TSH

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INTRODUCTION

The synthetic hormone levothyroxine (L-T4) has a chemical structure comparable to T4, and it is prescribed as substitutive therapy of hypothyroidism-associated conditions (1). Its absorption occurs through the intestinal mucosa at the level of the duodenum, jejunum and ileum (2).

Firstly, L-T4 was isolated from porcine thyroid extracts (3), in 1914. Until the mid-1950s, desiccated thyroid extract was the only treatment of hypothyroidism; then synthetic L-T4 entered the market in the tablet formulation (4).

The frequency of hypothyroidism is higher in women, especially over 60 years, and its diagnosis can be done by measuring thyroid-stimulating hormone (TSH) and T4 levels by blood tests (1). Hypothyroidism is commonly caused by a low iodine intake in countries with severe iodine deficiency, and autoimmune thyroiditis, or treatment with radioiodine, or thyroidectomy, in developed countries (5–8). Drugs, such as tyrosine kinase inhibitors, are a novel cause of primary hypothyroidism (9).

At TSH-suppressive doses, L-T4 is used in patients with thyroid cancer to decrease/stop its growth (10), while in presence of nodular goiter its administration is controversial (11).

Since slight changes in blood levels can lead to treatment failure or iatrogenic thyrotoxicosis (12), the individualization of oral T4 treatment is necessary. The L-T4 daily dose is chosen according to the main cause of hypothyroidism, the therapeutical target [i.e. replacement or TSH suppressive treatment], and the patients' body weight (13).

The supply of more sensitive TSH assays has progressively conducted to the reduction of L-T4 dose for replacement and TSH-suppressive treatments (14). The dosage of 1.5–1.7 μg/kg body weight/day is now considered as the optimal daily L-T4 replacement dose, which can normalize TSH levels in most hypothyroid patients (15). Despite this, about 20%–50% of patients do not respond to L-T4 (16) owing to different interfering issues (17), and need an increased dose, and monitoring (18). Some patients are not compliant with the prescribed regimen, causing a condition of pseudomalabsorption, and once excluded it, an altered intestinal absorption of L-T4, due to gastrointestinal disorders or interfering drugs, is considered the principal cause of refractory hypothyroidism (17).

In the era of precision medicine, therapies should be individualized and the characteristics of drugs should be evaluated accurately during a chronic treatment.

L-T4 TABLET MALABSORPTION

A randomized, prospective study was performed to compare L-T4 ingestion after an overnight fast, 60 min prior to breakfast, or at breakfast. In case of L-T4 administered at breakfast, TSH was higher than while fasting, leading to the conclusion that it is advisable to ingest L-T4 in a fasting state, to avoid the interference on L-T4 tablet absorption caused by food and beverages (19).

Another study compared L-T4 ingestion with breakfast, versus 60 min before breakfast, versus bedtime. In this study it was shown that the 1 h before breakfast ingestion has not only lower TSH values but also substantially more uniform outcomes of TSH (20).

The lack of comparison of L-T4 ingestion 30 min, vs. 60 min before breakfast in the literature, suggests that this is an area of future research.

A study demonstrated that milk is also one of the interfering beverages that are frequently ingested with breakfast (21).

For example, L-T4 absorption is reduced if ingested 10 min before drinking coffee or with dietary fiber (22).

Since L-T4 tablets are composed by a stable salt, sodium L-T4, and different excipients, after its ingestion, the acid gastric pH is necessary to dissolve the tablet and remove sodium, to convert L-T4 into a lipophilic molecule (23, 24). The ingestion of L-T4 plus water improves drug absorption that is higher in the first 3 h, especially within the second hour (25). Approximately 70% of tablet L-T4 is absorbed (1).

Moreover, bariatric surgery can lead to medication malabsorption, in particular for L-T4 and cyclosporine, as shown in jejunoileal bypass, biliopancreatic diversion, and gastric bypass/gastroplasty (26).

Some drugs can alter L-T4 absorption, increasing the gastric pH [i.e. proton-pump inhibitors (PPIs), sucralfate, aluminum-containing antacids], preventing the dissolution of the tablet, others can bind L-T4 creating insoluble complexes (i.e. iron or calcium salts, ferrous sulfate, phosphate binders, calcium carbonate, bile acid sequestrants), while the mechanism of action of raloxifene is unknown (27).

Furthermore, various intestinal or gastric disorders, such as atrophic gastritis, Helicobacter pylori (HP) infection, celiac disease (CD), lactose intolerance (LI), and inflammatory bowel disease, can alter L-T4 tablet absorption (1).

NEW ORAL L-T4 FORMULATIONS

Patients refractoriness to a "normal dose" of L-T4 (27) has led to the development of novel hormonal preparations, the liquid formulation and soft gel capsule, to achieve an improved performance for this broadly advised drug.

Liquid L-T4

The liquid preparation contains L-T4, ethanol, and glycerin, and it has the advantage that a gastric phase of dissolution of the tablet is not necessary (28), and it has a shorter mean time to attain the higher concentration than the tablets (29).

Also in newborns with congenital hypothyroidism, the reduction of TSH values observed with liquid L-T4 was higher vs. tablets (30, 31). Moreover, a first meta-analysis suggested that subjects receiving L-T4 tablets with suboptimal TSH values can achieve the desirable TSH after the switch to liquid L-T4 using the same dosage (32), and a second one indicated that the effectiveness of liquid L-T4 is higher (vs. tablets) in patients having or not having malabsorption in replacement or suppressive treatment (33).

Another study demonstrated a greater stability in the thyroid profile of hypothyroid elderly patients treated with liquid thyroxine as opposed to those being treated with tablet formulation over 5 years of follow-up (34). The state of pregnancy needs an adaptation of thyroid function, and for this reason hypothyroid women on replacement treatment with L-T4 usually require an increase of the dose of 30–50% at the beginning of pregnancy. A better control of serum TSH with

the L-T4 liquid formulation was observed also in pregnant women (35). Thirty-one hypothyroid pregnant women who suffered from Hashimoto's thyroiditis (HT) were involved in the study. Fourteen patients were in replacement therapy with liquid L-T4 and 17 were on tablets. Pre-pregnancy TSH and FT4 levels were similarly distributed in the two groups. During pregnancy, 8/31 (25.5%) of the women had to increase the dosage of L-T4. Among them, 7/17 (41.2%) were on L-T4 replacement therapy with tablets, and 1/14 (7.1%) with liquid L-T4. The mean dose of L-T4 from baseline to delivery was significantly increased only in women on tablets, as opposed to those on liquid therapy (35).

Furthermore, the effectiveness of liquid L-T4 was evaluated in hypothyroid patients with no malabsorption or drug interference. The stability of TSH levels was improved with liquid L-T4 with respect to tablets in these patients (36, 37).

The liquid L-T4 permitted to control better the stability of TSH levels also in patients who underwent thyroidectomy for cancer (38), or after bariatric surgery (39).

Soft Gel Capsule

Sodium L-T4 is dissolved in water and glycerin in the soft gel capsule, and put in a gelatin matrix, to protect the active ingredient from degradation. It does not contain lactose, gluten, alcohol, sugar, or dyes (28).

A study evaluated whether the soft gel capsule formulation overcomes the malabsorption associated with the consumption of coffee, recruiting eight patients (including one with hypothyroidism, and the remaining seven patients under L-T4 suppressive doses in treatment for benign nodular goiter or recurrence of nodules after thyroidectomy) (40). The subjects were switched from tablets to capsule at the same L-T4 dosage for 6 months, with more consistent TSH outcomes (40).

A study investigated the daily requirement of L-T4 in 103 patients who underwent thyroidectomy, showing that the L-T4 requirement for attaining normal TSH values was not significantly different between soft gel capsules and tablets L-T4. However, although the TSH levels were within the normal range with both formulations, a statistically significant reduction of about 28% in the mean circulating TSH was observed with the soft gel formulation vs. tablets (41).

Another paper evaluated the new preparations of oral L-T4 in central hypothyroidism, reporting that liquid or soft gel L-T4, at the same dose as tablet L-T4, permit to obtain target serum FT4 levels above the midnormal range value (vs. tablets), suggesting the more favorable pharmacokinetics profile of either novel formulations in comparison with the tablet formulation (42).

Recently, a study evaluated the effect of switching from tablets to soft gel capsule in hypothyroid patients without an increased need of L-T4 (43). Circulating TSH level was in the normal range in 11/18 pts receiving L-T4 tablets, while after the switch in 16/18, and the median TSH was lower than that obtained with the classical formulation (43).

The above mentioned studies showed that liquid, and soft gel capsule L-T4 permit to maintain better the TSH stability (in the reference range) in hypothyroid patients.

LIQUID L-T4 AND FOOD INTERFERENCE

Liquid L-T4 can be administered in few patients who are unable to swallow capsules or tablets, and this is one of its major benefits. Thyroid hormones and TSH values were evaluated in subjects taking L-T4 in tablets, in comparison to patients receiving the liquid preparation with an enteral feeding tube, and it was shown that liquid L-T4 can be given by a feeding tube, facilitating its administration by nurses (31).

Other studies have investigated food interference with L-T4 absorption (44, 45). A placebo-controlled, double-blind, crossover, randomized trial enrolled 77 hypothyroid patients, who received randomly the liquid L-T4 at breakfast, or at least 30 min before it (46). TSH and thyroid hormones values were comparable in both cases, suggesting that the liquid L-T4 preparation can be swallowed at breakfast, in this way ameliorating the therapeutic compliance (46).

The lack of comparison of L-T4 ingestion 30 min, vs. 60 min before breakfast in the literature (even if guidelines suggest at least 30 min) encourages future research in this area.

LIQUID L-T4 FORMULATIONS IN DISORDERS THAT IMPAIR GASTRIC ACIDITY

Different gastrointestinal disorders, that interfere with the normal gastric acid secretory activity, decrease the efficacy of tablet L-T4 (47–49), and liquid L-T4 has been evaluated in these patients.

The acid environment of the stomach can be altered in presence of HP-associated gastritis, atrophic gastritis, or in patients who are taking PPIs (50).

The presence of HP influences drugs bioavailability, the level of gastric pH and of the inflammatory condition that occurs as a result of the disease itself (51, 52), leading to the uncertainty about the dosage that is absorbed. Patients with an altered acid secretion need an elevated dose of L-T4; the necessary daily dose was higher (of approximately 22–34%) in presence of atrophic gastritis, HP-related gastritis, or both (23).

A study compared the clinical effectiveness of tablet and oral liquid L-T4 in naïve hypothyroid patients with HP-infection. In patients with HP infection after 3 months (before HP eradication), subjects treated with liquid L-T4 showed a greater TSH reduction and a greater homogeneity in the TSH values, compared to L-T4 tablet. These results suggested that L-T4 liquid formulation may produce a better clinical response compared to the tablet formulation in hypothyroid subjects with HP infection (50).

L-T4 malabsorption is also a possible issue in presence of autoimmune atrophic gastritis (23, 53).

A study involved 391 patients with autoimmune thyroid disease administered with L-T4; 40% of them had positive parietal cell antibodies (PCA) and higher tablet L-T4 requirement in comparison to patients with negative PCA

(1.24 ± 0.40 μg/kg vs. 1.06 ± 0.36 μg/kg). The required dose of tablet L-T4 was even higher in presence of an evident gastritis on histology (54).

A case series evaluated five patients with autoimmune gastritis, and hypothyroidism, receiving L-T4 tablets, who were switched to the same dosage of liquid L-T4. After the switch, circulating TSH normalized in all patients. In four of them, who were switched back to L-T4 tablets (same dose), TSH worsened, leading to the hypothesis that liquid L-T4 can circumvent the pH impairment associated with atrophic gastritis (55).

The secretion of gastric acid is blocked also by PPIs that bind covalently to the H^+/K^+ATPase enzyme (56). A crossover study, conducted in patients in whom tablet L-T4 absorption was impaired by PPIs, demonstrated a significant decrease in circulating TSH following the switch from the tablet preparation to the liquid one, at the same daily dose, maintaining the co-ingestion of PPI (57).

LIQUID L-T4 IN INTESTINAL MALABSORPTION

Bariatric Surgery

Drug malabsorption can derive from bariatric surgery (58).

Drug dissolution and solubility may be potentially altered in restrictive procedures that increase gastric pH in the newly created stomach.

In addition, highly lipophilic drugs are more likely to be affected because they are often dependent upon the availability of bile acids to enhance solubility. Often, these agents also undergo enterohepatic recirculation. Bypass of the upper small intestine limits the mixing of such drugs with bile acids to the common (post-anasatamotic) limbs of the distal small intestine. Jejunoileal bypass may also result in bile acid wasting (26).

Seventeen hypothyroid patients [who had been successfully treated with L-T4 tablets for more than 1 year prior surgery (13 Roux-en-Y gastric bypasses (RYGB); 4 biliary pancreatic diversions (BPD))] had elevated TSH levels from 3-8 months after surgery. Following the switch from tablets to liquid L-T4 (30 min prior to breakfast, same dose), TSH significantly decreased both in patients who underwent RYGB, or BPD, preventing the issue of malabsorption in BPD-treated patients, and in agreement with previous data obtained in patients who underwent RYGB. This leads to hypothesize that liquid L-T4 can bypass the malabsorption issue associated with bariatric surgery (39).

Lactose Intolerance

LI should be evaluated among the gastrointestinal diseases leading to L-T4 malabsorption. In presence of LI, to restore euthyroidism or reduce the necessary dose of L-T4 (in tablets that usually contain lactose as an excipient), a low lactose diet, and/or a lactose-free L-T4 formulation, should be given (59, 60).

From 2009 to 2012, a cohort study was performed to analyze the replacement L-T4 dose (using tablets containing lactose) in 34 hypothyroid subjects with HT and LI, who were not compliant with a lactose-free diet (48). In presence of HT, the target TSH was achieved with a median L-T4 dose of 1.31 μg/kg/day. In patients with HT and LI, 5/34 reached the desired TSH with 1.29 μg/kg/day L-T4 (a similar dose). In the other 29 patients, the L-T4 dosage was gradually increased and the target TSH was achieved at a median L-T4 of 1.81 μg/kg/day ($P<0.0001$). In 6/29 patients, other gastrointestinal disorders were reported, and their median L-T4 dose was more elevated (2.04 μg/kg/day; $P=0.0032$). In the other 23/29 patients with LI, a median L-T4 dosage of 1.72 μg/kg/day ($P<0.0001$) was necessary to achieve target TSH levels. These data showed that in presence of LI the needed dose of L-T4 increased in a significant manner in hypothyroid patients (48).

The case of five patients with hypothyroidism and LI in treatment with an adequate dosage of L-T4 tablets (containing lactose) was reported, in whom the switch to a liquid L-T4 preparation (without lactose) at the same dosage caused the normalization of serum TSH. In 3 of them, TSH worsened again, after switching back to the tablets (61).

Celiac Disease and Gluten Sensitivity

Another cause of **tablet** L-T4 malabsorption is CD, an immune-mediated enteropathy, developing in genetically susceptible subjects after the ingestion of wheat gluten, that can regress after the removal of gluten from the diet (62). Celiac patients with elevated TSH levels during L-T4 therapy showed an improvement after a gluten-free diet, thus revealing the importance of the alteration of the intestinal barrier in CD.

A study evaluated hypothyroid patients with concurrent CD. A total of 500 hypothyroid patients were enrolled and 29% of them needed a L-T4 dose ≥125 μg/day. CD was detected in nine patients. Eight/nine (89%) patients with CD required ≥125 μg/day of L-T4. Patients requiring ≥125 μg/day of L-T4 had a significantly higher risk of CD ($P<0.001$), and CD was found in 5.6% of them (63).

A study evaluated replacement tablet L-T4 dose in 35 patients with hypothyroidism, chronic autoimmune thyroiditis and atypical CD, as defined by the American Gastroenterological Association (47). In patients diagnosed with only HT, the target TSH level was attained after 5 ± 2 months of treatment with a median L-T4 dose of 1.31 μg/kg/day. Higher levels of TSH were observed in patients with HT and CD, following a comparable period and dose of L-T4. In 21 CD patients, target TSH was reached after 11 ± 3 months of gluten-free diet with no changes in the L-T4 dose. In the other 14 patients, noncompliant with the gluten-free diet, target TSH has also been attained but at higher L-T4 dosage ($P=0.0002$) than in hypothyroid patients without CD. These data suggested that atypical CD raises the need for L-T4, and the gluten-free diet or an increasing L-T4 dose can reverse this effect (47).

Intestinal Parasitosis

Another cause of L-T4 malabsorption is chronic intestinal parasitosis. *Giardia lamblia* is one of the most prevalent human intestinal parasitic protist and can induce malabsorption of drugs

and nutrients (causing anemia, weight loss, and growth retardation) (64). The case of a 57-year-old woman with hypothyroidism, well-controlled for the preceding 6 years, but unexpectedly showing poor hormonal control and abdominal symptoms, was reported. An adequate management of thyroidal function was obtained only after treatment of intestinal giardiasis (65). Moreover, the case of a 63-year-old woman with autoimmune hypothyroidism, well-replaced with tablet L-T4, who then became suddenly no more euthyroid, was shown (2). The patient reported the onset of acute gastrointestinal symptoms, associated with an increase in TSH levels. Owing to the suspect of a malabsorption disease, a switch from L-T4 tablets to a liquid formulation was suggested, to reach an optimal therapeutic target although the persistence of gastrointestinal symptoms, and thyroid hormones normalized. Further investigations permitted to diagnose a malabsorption syndrome due to *Giardia lamblia*, and liquid oral L-T4 solved the problem of its decreased absorption, even if the exact mechanism of action in the case of giardiasis is still not known (2).

These data suggest that giardiasis should also be considered in the assessment of the "difficult patient" with hypothyroidism, after ruling out non-adhesion and use of interfering drugs, in particular in areas, such as Brazil and other developing countries, with high prevalence of the infection, and in patients with symptoms of giardiasis (abdominal pain, diarrhea, weight loss, anemia) or with personal or family history of giardiasis (65).

L-T4 SOFT GEL CAPSULE IN GASTROENTERIC MALABSORPTION

Few studies evaluated soft gel capsule preparation in enteric malabsorptive disorders. These preparations have been proven to have a different dissolution profile and absorption with respect to the traditional L-T4 tablet form by pharmacokinetic studies (24, 66).

Another study (67) compared L-T4 tablets and soft gel preparation in 31 patients with gastric-related L-T4 malabsorption. Inclusion criteria were: 1. patients with an increased need of thyroxine; 2. patients with a histologically diagnosed gastric disorder impairing gastric acid secretion. Patients took (since >2 years) L-T4 tablets, and then were switched to soft gel L-T4 capsule at a lower dosage (median reduction of T4 dose of 17%). Circulating TSH and FT4 were evaluated again in the following months. Even with the reduced dosage of L-T4, at each point of evaluation, median TSH levels were similar in 21 patients; whereas TSH was significantly higher in the remaining 10. It was concluded that a lower dosage of soft gel L-T4 capsule with respect to L-T4 tablet is necessary to preserve the therapeutic target in approximately 2/3 of subjects with altered gastric acid secretion (67).

The case of a woman with HT and hypothyroidism, in whom the altered absorption of L-T4 tablets, caused by PPIs, was corrected by the switch to soft gel capsule, was shown. Circulating TSH was lower than under the same dose of tablets. Switching back to tablets, serum TSH increased and then dropped when the dose was finally increased again (68).

A retrospective analysis was performed in 99 hypothyroid patients [of whom 24 reporting gastrointestinal comorbidity, in particular gastroesophageal reflux disease (11.1%), CD (6.1%), gastric bypass (3%)] who were switched from tablets to soft gel L-T4 capsule. Among the 99 patients studied, 51.5% had no documented changes in TSH status after the switch ($P<0.0001$), more than 26% of patients had a documented improvement in their TSH status (26/99), and only a minority of patients (22.2%) experienced a worsening of their TSH status post-switch. Improved hypothyroid symptom control was shown in 61.6% of patients ($P<0.0001$) (69).

CONCLUSION

The development of new oral formulations (the liquid preparation, and the soft gel capsule) represents the most recent advance regarding L-T4 therapy. The treatment of hypothyroidism with L-T4 tablets can lead to an improper (elevated or suppressed) control of TSH in approximately 10-15% of patients (even with a correct L-T4 dosage) (1). The improperly elevated TSH, caused by the above reported conditions, is usually managed increasing the L-T4 daily dose, and a following re-evaluation of TSH upon 2–6 months. However, the increase of the L-T4 daily dosage may sometimes cause iatrogenic hyperthyroidism, in particular when the underlying disorders (i.e., a gluten free diet) are cured, or with the stop of interfering drugs.

Liquid L-T4 can be given to patients unable to swallow capsules or tablets, and this is one of its major benefits. Moreover, it has been reported that liquid L-T4: 1- overcomes the food and beverages interference, caused by food, coffee, or breakfast, observed with L-T4 tablets; 2- circumvents malabsorption induced by a raised gastric pH in atrophic gastritis, or due to PPI treatment, or in patients with HP infection; 3- can bypass the issue of malabsorption in patients who underwent bariatric surgery, or in patients with LI; 4- maintains better the TSH stability (in the reference range) in hypothyroid patients with a diagnosis of CD and gluten sensitivity, or intestinal parasitosis, even if properly treated for those conditions.

Soft gel L-T4 have been evaluated by few clinical studies, reporting encouraging data in patients with gastric- or coffee-related T4 malabsorption, or hypothyroid patients without malabsorption.

Further studies are ongoing to evaluate liquid L-T4, or soft gel L-T4, in other conditions of altered L-T4 absorption. Since enough data from randomized clinical trial are lacking, prospective, randomized studies are needed.

AUTHOR CONTRIBUTIONS

PF, SMF, and AA conceived the paper. All authors contributed to the article and approved the submitted version.

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GENERAL COMMENTARY
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Commentary: L-T4 Therapy in Enteric Malabsorptive Disorders

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Keywords: hypothyroidism, levothyroxine therapy, malabsorption disorders, gastrointestinal diseases, cystic fibrosis

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A Commentary on

L-T4 Therapy in Enteric Malabsorptive Disorders
By Fallahi P, Ferrari SM, Elia G, Ragusa F, Paparo SR and Antonelli A (2021). Front. Endocrinol. 12:626371. doi: 10.3389/fendo.2021.626371

We really appreciated the paper recently published in Your Journal *Fallahi P, Ferrari SM, Elia G, Ragusa F, Paparo SR, Antonelli A. L-T4 Therapy in Enteric Malabsorptive Disorders. Front Endocrinol 2021;12:626371* (1) about the important clinical issue of levothyroxine (L-T4) malabsorption in patients affected by gastrointestinal disorders. The introduction of novel formulations, both the liquid ones and the soft gel capsules, has dramatically changed the outcomes of replacement therapy in these categories, allowing to achieve more adequate levels of TSH and better quality of life due to the reduced need for continuous dose changes.

The review by Fallahi and coworkers analyzed the impact of a wide spectrum of intestinal disorders on T4 treatment efficacy, in keeping with the interfering mechanisms and the pharmacologic features of T4 preparations. Herein we would like to point out, for the sake of completeness, that our research group has recently provided evidence that cystic fibrosis represents another cause of intestinal L-T4 malabsorption and that the novel formulations are efficacious in hypothyroid patients with CF to overcome malabsorption (2).

Cystic fibrosis (CF) is an autosomal recessive disease due to mutations of CF transmembrane conductance regulator (CFTR) gene on chromosome 7, which encodes an ion channel. When CFTR function is impaired, the consequent defect leads to an abnormal transport of chloride ions and bicarbonate in many organs and tissues. CF equally affects both sexes with a greatly variable prevalence depending on ethnicity, being estimated 1/1,800 to 1/5,000 in European Caucasians (3). Over the last few decades, the average lifetime and the life expectancy of CF patients has significantly increased, due to both an early diagnosis and specialized treatment in early stages of disease (4). Beside the peculiar lung involvement, CFTR mutations also interest pancreatic and biliary duct cells, causing defective bile flow and thick biliary secretion, pancreatic exocrine insufficiency, and nutrients malabsorption, finally leading to diabetes mellitus and biliary fibrosis (3). The above-mentioned elements can also contribute to drug malabsorption creating difficulties into reaching

optimal therapeutical targets, like it is observed in hypothyroid patients in whom changing conditions and illnesses can determine the need to precisely adjust the doses of synthetic thyroid hormone.

We recently reported on the absorption profile of L-T4 in two patients affected by CF, a 44-year-old female, and a 39-year-old male, respectively, both in a state of post-surgical hypothyroidism (2). These subjects did not reach adequate TSH levels on weight-based doses of L-T4, so in order to analyze this finding we performed an absorption test by the administration of 600 ug of L-T4, measuring TSH, T4, and FT4 concentrations up to 4 h after drug ingestion. After LT4 load, T4 and FT4 remained below the lower reference limit in the first patient, while FT4 only slightly increased in the second one, confirming a true malabsorption in both subjects. The initiation of liquid LT4 formulation in both patients, at progressively lower daily doses (less than 2.0 ug/kg/d), led to target TSH ranges stable at the subsequent evaluations.

As demonstrated by Fallahi et al. and our experience, many factors can impair L-T4 absorption at gastrointestinal level, and in particular several diseases like *Helicobacter pylori* infection, celiac disease, inflammatory bowel diseases (IBDs), etc. In this context, CF must be mentioned since the mutations of CFTR gene correlate to pancreatic insufficiency, reduced biliary salt production, abnormal intestinal transit, and chronic intestinal inflammation, that ultimately concur to malabsorption in variable degrees, depending on disease severity. In particular, the increased L-T4 requirement associated with CF could be mainly due to defects in bile production and excretion, since the dysfunctional CFTR protein causes thickened secretions and biliary obstruction from plugging. This alteration not only leads to hepatocyte damage, with inflammation and fibrosis within the portal tracks, but can also contribute to suboptimal therapeutic regimens (5). Also, the lack of pancreatic enzymes and the consequent steatorrhea, as well as the abnormalities in intestinal transit, may result in increased fecal losses of L-T4, accounting for malabsorption (6). Moreover, some recent studies have also hypothesized a direct involvement of the gastrointestinal tract probably due to a diffuse inflammation of the small bowel, as suggested by the finding of diffuse mucosal lesions and high levels of fecal calprotectin in some CF patients (7).

Prior to our report, there are only few data in the literature concerning this clinical issue. It is worth mentioning the experience described by Depasse et al. in the early '90s, a case of congenital hypothyroidism associated with CF, in which the two coexisting diseases complicated the management of thyroid dysfunction (6). In this male newborns the impaired pancreatic secretion and gastrointestinal transit abnormalities secondary to meconium ileus resulted in decreased absorption of L-T4, that was partially overcome by the administration of pancreatic enzymes, even if with greater doses than those required in newborns with congenital hypothyroidism to normalize TSH and FT4 levels (6). Recently, in our patients the use of the liquid L-T4 formulation with its improved pharmacokinetics has been demonstrated to bypass all the cited limitations, and permitted to reach target TSH levels that were missed by the conventional tablet formulation, as reported in other conditions (8). By shifting patients towards liquid L-T4 formulation we reached stable TSH levels, reducing the burden of frequent clinical and biochemical evaluations for the patients.

In summary, CF needs to be included in the list of enteric diseases involved in L-T4 impaired absorption, that should be always taken into account in these patients. L-T4 oral liquid formulation can overcome, at least in part, the reduced absorption of L-T4 in CF patients, leading to more tailored choices and a better management of hypothyroidism.

AUTHOR CONTRIBUTIONS

GG and RR conceived the commentary structure and performed the review of literature; RR, AC, and SC finally revised the manuscript. All authors contributed to the article and approved the submitted version.

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MINI REVIEW
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The Stability of TSH, and Thyroid Hormones, in Patients Treated With Tablet, or Liquid Levo-Thyroxine

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Approximately, 5% of the population is affected by hypothyroidism, mainly women and persons aged more than 60 years. After the diagnosis of hypothyroidism the usual therapy is tablet levothyroxine (L-T4), with a monitoring of the thyroid-stimulating hormone (TSH) level in primary hypothyroidism every 6–8 weeks and L-T4 is adjusted as necessary to reach an euthyroid state. Once TSH is stabilized in the normal range, it is recommended to conduct annual testing in the treated subjects to warrant suitable replacement. More recently advances regarding L-T4 treatment are the introduction of new oral formulations: the liquid solution, and soft gel capsule. The soft gel capsule permits a quick dissolution in the acid gastric pH. The liquid preparation does not require an acid gastric environment. Many pharmacokinetic studies demonstrated a more rapid absorption for the liquid L-T4, or capsule, than with tablet. Many studies have shown that the liquid, or capsule, formulations can overcome the interaction with foods, drugs or malabsorptive conditions, that are able to impair the tablet L-T4 absorption. Lately studies have suggested that liquid L-T4 can permit to maintain more efficiently normal TSH levels in hypothyroid patients in the long-term follow-up, than tablet L-T4, both in patients with malabsorptive states, and in those without malabsorption. Further large, prospective, longitudinal studies are needed to evaluate the stability of TSH, in hypothyroid patients treated with different L-T4 formulations.

Keywords: thyroid-stimulating hormone (TSH), hypothyroidism, soft gel capsule L-T4, liquid L-T4, malabsorption, levothyroxine

INTRODUCTION

In physiological conditions, thyroid hormones (TH) are produced by the gland and their synthesis depends on normal iodide transport. Approximately 10%–20% triiodothyronine (T3) and 80%–90% thyroxine (T4) are secreted by the thyroid, then T4 is converted to T3 by deiodinase enzymes (1). T4 functions as a pro-hormone, and T3 is about four to five times more potent than T4 (2). TH regulate protein synthesis, energy metabolism, and the sensitivity to other hormones (3).

Thyroid-stimulating hormone (TSH), secreted by the pituitary, regulates TH output from the thyroid, and it is controlled by thyrotropin-releasing hormone (TRH), secreted by the hypothalamus (4). A negative feedback controls the release of TH: TSH secretion is suppressed if free T3 (FT3), or free T4 (FT4) levels are elevated, and the same happens for the production of TRH by the hypothalamus (2).

The synthetic hormone levothyroxine (L-T4) has a structure comparable to T4, and it is done as substitutive therapy of hypothyroidism-associated conditions (2). It is absorbed in duodenum, jejunum and ileum (5).

The frequency of hypothyroidism is higher in women, especially over 60 years, and it can be diagnosed measuring serum TSH and free T4 values (2). Hypothyroidism can be caused by different conditions (6–9): 1) A low iodine intake in countries with severe iodine deficiency; 2) autoimmune thyroiditis that is the most common cause in iodine sufficient countries; 3) thyroidectomy; 4) radioiodine treatment for hyperthyroidism. Drugs, such as tyrosine kinase inhibitors, and immune checkpoint inhibitors, are a novel cause of primary hypothyroidism (10, 11).

The L-T4 daily dose is chosen according to the principal cause of hypothyroidism, the therapeutic target, and the patients' lean body mass (12). Slight changes in blood levels can lead to treatment failure or iatrogenic thyrotoxicosis (13), for this reason the individualization of oral T4 treatment is necessary.

After the diagnosis of hypothyroidism the usual therapy is tablet L-T4; TSH is monitored in primary hypothyroidism every 6–8 weeks, and L-T4 is adjusted as necessary to reach euthyroidism. The optimal daily L-T4 replacement dosage is 1.5–1.7 μg/kg body weight/day, that can normalize TSH in most hypothyroid patients (14). Anyway, ~20%–50% of patients on L-T4 do not attain a normal TSH in cross sectional studies (15) and need an adjustment of therapy (16), due to various interfering issues (17).

Once the TSH is stabilized in the normal range, it is recommended to conduct an annual testing in treated subjects to warrant suitable replacement. A study retrospectively evaluated 452 patients treated for hypothyroidism, assessing the number of those who successively had therapeutic and non-therapeutic TSH values 10–14 months later (18). The percentage of normal repeat TSH values significantly decreased with increasing medication dosage (P=0.01). Considering patients whose maintenance dose was <75 μg/day, 90.8% had normal repeated TSH values, in comparison to 77.5% of those needing ≥125 μg/day, who had significantly lower odds of normal repeated TSH [odds ratio, 0.31; 95% confidence interval (CI), 0.13–0.76; P=0.01]. The authors concluded that the dose of TH replacement was predictive of normal TSH values, and patients taking ≥125 μg/day L-T4 are less likely than those needing lower doses to have a normal repeated TSH value in 1 year (18).

More recently, a study investigated whether any clinical predictors exist that can distinguish patients who could be monitored safely, less frequently than yearly (19). Seven hundreds and fifteen patients treated for hypothyroidism, with normal TSH value while taking L-T4, were retrospectively evaluated. L-T4 dosage >125 μg/day had an augmented hazard ratio of 2.4 (95% CI, 1.7–3.4; P<0.0001) for time to first follow-up elevated TSH value, but doses lower than that did not raise the hazard ratio. One year after the first normal TSH, 91.1% of patients receiving ≤125 μg/day had a persisting normal TSH, while only 73.3% of patients taking >125 μg/day did. The authors concluded that patients receiving daily dosages >125 μg/day of L-T4 have more difficulties to maintain stable TSH values over time than those needing lower dosages of L-T4 (19).

The aim of this review is to evaluate the stability of TSH, and TH, in patients treated with tablet, or liquid L-T4.

We searched relevant and recently (from 2000) published papers on PubMed using principally the terms "levothyroxine therapy", "tablet levothyroxine", "liquid levothyroxine", "soft gel capsule L-T4", "levothyroxine malabsorption", in combination with "hypothyroidism", and "TSH".

NOVEL ORAL L-T4 PREPARATIONS

Some patients are not compliant with the prescribed L-T4 regimen, and this can cause a condition of pseudo-malabsorption. Moreover, resistance to TH (RTH) is a rare autosomal dominant disorder that leads to elevated free TH levels, in the presence of normal or increased serum TSH concentrations, if it is generalized because both the pituitary and peripheral tissues are then partially resistant (20). Once those are excluded, an altered intestinal absorption of L-T4 (caused by gastrointestinal disorders, some nutrients, or drugs) is considered the principal cause of refractory hypothyroidism. Moreover, the case of a 49-year-old patient suffering from hypothyroidism refractory to oral LT-4 substitution after total thyroidectomy and radioiodine therapy for papillary thyroid cancer (PTC) was reported (21). Furthermore, three cases of critically ill patients with prolonged respiratory failure, suppressed mental status and unexplained hypotension were reported, who showed normal or mildly abnormal TSH values and free thyroxine markedly suppressed. After initiation of intravenous L-T4, the patients could be weaned off vasopressors and were successfully extubated shortly thereafter, suggesting that the early recognition and treatment of hypothyroidism in presence of a critical illness can contribute to recovery from hypotension or the need for mechanical ventilation (22). The improperly elevated TSH, caused by such conditions, is managed by the increase of the L-T4 daily dosage, that can cause iatrogenic hyperthyroidism, especially when the underlying disorders (i.e., with a gluten-free diet) are cured, or

the effect of interfering drugs is stopped. Patients refractoriness to a "normal dose" of L-T4 (23) has led to novel hormonal formulations that could permit to attain an improved performance of this drug: the liquid formulation and soft gel capsule.

Liquid L-T4

The liquid formulation is bioequivalent with the traditional one, but it has a shorter mean time to attain the higher concentration than soft gel capsule or tablets (1.96 vs. 2.38 vs. 2.25 h) (24), and it contains L-T4, ethanol, and glycerin; with respect to tablets, it does not require an acid gastric pH to dissolve it (25).

Liquid formulation effectiveness has been evaluated in two meta-analyses. The first meta-analysis suggested that subjects receiving L-T4 tablets with suboptimal TSH values can achieve the desirable TSH following the switch to liquid L-T4 using the same dose (26), and the second indicated that the efficacy of liquid L-T4 is higher (vs. tablets) in patients having/or not malabsorption in replacement or suppressive treatment (27).

The prescription of liquid L-T4 has been evaluated in newborns with congenital hypothyroidism (28). Seventy-eight patients were enrolled, of whom half received liquid L-T4 and the other half L-T4 in tablets. All subjects had similar birth weight, gestational age, etiology, and severity of congenital hypothyroidism, screening TSH, median initial L-T4 dose, and age at onset of therapy. FT4 levels normalized within 10 days of therapy, and TSH within 7–10 days, in 87% of patients receiving the liquid formulation and in 82% administered with tablets. Albeit L-T4 dose and free T4 levels were comparable, patients taking liquid L-T4 had significantly lower TSH values in comparison to those receiving tablets, at 7–10 days (P=0.05) and 6–8 months (P=0.043) of therapy. The authors concluded that the TSH inhibition rate observed with liquid L-T4 could be related to a major absorption with respect to tablets (28). These data were confirmed also by another study (29).

Moreover, it has been shown that the L-T4 solution can control better serum TSH values compared to tablets also in elderly (30), and in pregnant women (31).

Soft Gel Capsule

Sodium L-T4 is dissolved in water and glycerin in soft gel capsule, and put in a gelatin matrix, to protect the active ingredient from degradation. It does not contain lactose, gluten, alcohol, sugar, or dyes (25).

Soft gel L-T4 was evaluated by few clinical studies. A study evaluated whether soft gel capsule formulation is able to overcome the malabsorption associated with the consumption of coffee (32). Eight patients with this issue were recruited, including one with hypothyroidism. The subjects were switched to capsule at the same L-T4 dosage for 6 months. All patients assumed the capsule with water, on days 1–90 patients followed a proper habit, taking coffee 1h later the drug assumption; whereas on days 91–180 they followed an improper habit by taking coffee ≤5 min later after the capsule ingestion. In seven patients after the switch, TSH values were 0.41 ± 0.46 mU/ml in those following a proper habit vs. 0.28 ± 0.20 pre-switch, and 0.34 ± 0.30 in patients following an improper habit vs. 1.23 ± 1.47 pre-switch (P<0.001). These findings indicated that soft gel capsule is effective in patients who are not able or do not wish to modify their improper habit of taking L-T4 (32).

A study investigated the daily requirement of L-T4 in 103 patients who had undergone to thyroidectomy. The L-T4 dose necessary to reach normal TSH values was similar between the two types of formulations (soft gel capsules and tablets), but a statistically significant decrease of about 28% in the mean TSH was reported with the soft gel in comparison to tablets (33).

Recently, a study evaluated the effect of switching from tablets to soft gel capsule in hypothyroid patients, without an increased need of L-T4 (34). Hypothyroid subjects with no confirmed malabsorption had an improved TSH after 3 months from the switch. Circulating TSH level was in the normal range in 11/18 patients receiving L-T4 tablets, while after the switch in 16/18, and the median TSH was lower than that obtained with the classical formulation (34).

STABILITY OF TSH, AND TH, IN PATIENTS TAKING TABLETS, OR LIQUID L-T4

L-T4 is prescribed all over the world as substitutive therapy in case of hypothyroidism, and in patients affected by thyroid cancer after thyroidectomy (35). Even if the substitutive therapy with L-T4 has been used for >60 years, cross-sectional studies demonstrated that 40%–48% of patients receiving L-T4 are under- or over-treated (36, 37).

The recently marketed new formulations of L-T4, in comparison to tablets, lead to a significant decrease in TSH variability in hypothyroidism, in young and old people (30, 38).

Food Interference

A study compared the TH profile in patients treated with tablets or liquid L-T4 with an enteral feeding tube (29). The day after surgery, 20 euthyroid subjects who had undergone to total laryngectomy and thyroidectomy began L-T4, by an enteral feeding tube. Before administration, tablets were fragmented and enteral feeding was blocked for 30 min before and after L-T4 therapy, while the liquid solution was put immediately in the nasoenteric tube. The findings demonstrated that liquid L-T4 can be done through a feeding tube without the necessity of an empty stomach, ameliorating its administration by nurses (29). The reported data permit to demonstrate that one of the major benefit of liquid L-T4 is that it can be administered in patients unable to swallow capsules or tablets.

The food interference with L-T4 absorption has been evaluated also by other studies, for example the assumption of tablet L-T4 with coffee, or with water and then coffee within few minutes, can lead to an improper TSH response (39). After a casual identification of an euthyroid subject who erroneously assumed liquid L-T4 with coffee at breakfast, 54 patients were identified, taking the same dose of L-T4 30 min before breakfast. No significant differences in TH levels existed in patients consuming L-T4 at breakfast or 30 min before it for 3 and 6 months (39). Another study enrolled 61 patients, among whom 59 completed it, to compare L-T4 at

breakfast or 10 min before it, respect to L-T4 30 min before breakfast, with no clinically relevant differences with respect to the timing of administration (40). Moreover, a placebo-controlled, double-blind trial was conducted in 77 hypothyroid patients, who received randomly the liquid L-T4 at breakfast, or at least 30 min before it, with no significant differences in TSH and TH levels in both cases. The reported data indicated that the liquid preparation can be swallowed at breakfast, favouring the therapeutic compliance (41).

Moreover, a study assessed changes in quality of life (QoL) of 418 hypothyroid patients who were not satisfied with their therapy with L-T4 tablets. One hundred-ten patients (26.3%) complained of the timing of their L-T4 therapy (30–60 min before breakfast), and were switched from tablets taken 30–60 min before breakfast to liquid L-T4 at breakfast. An improved QoL, linked to the easier adherence to therapy, was reported by 66.6% of 102 patients who completed the study after the switch ($P<0.01$) (42).

Impaired Gastric Acidity

The presence of Helicobacter Pylori (HP) can negatively impact drugs bioavailability, and the level of gastric pH owing to the inflammatory condition associated with it (43, 44), leading to the unpredictability of the absorbed dosage. Patients with an impaired gastric acid need a higher daily dosage of L-T4, of approximately 22%–34%, in presence of atrophic gastritis, HP-related gastritis, or both (45).

Twenty-eight patients with HP infection and 15 without gastric alterations, treated with the same dosage of L-T4, in tablets for 9 months or oral liquid formulation for 6 months, respectively, were investigated (46). HP infection was eradicated after 3 months of L-T4 treatment. After 3 months (before HP eradication), subjects treated with the liquid formulation had a greater TSH reduction ($P=0.029$) and a greater homogeneity in the TSH values ($P=0.025$), with respect to tablets. At 9 months (after 6 months of HP eradication) mean TSH was lower in patients taking L-T4 tablet ($P=0.006$), while in the group of patients without gastric alterations, no differences were observed, at each time point, in the mean TSH, and TSH variations, between the two L-T4 formulations. The authors concluded that L-T4 liquid preparation can lead to a better clinical response (vs. tablets) in hypothyroid subjects with HP infection (46).

L-T4 malabsorption can occur also in presence of autoimmune atrophic gastritis (47). A study enrolled 391 patients with subclinical or clinical hypothyroidism associated with autoimmune thyroiditis administered with L-T4, and screened circulating parietal cell antibodies (PCA) as marker of autoimmune gastritis (48). A higher L-T4 requirement was shown in patients with positive PCA vs. those with negative PCA (1.24 ± 0.40 μg/kg vs. 1.06 ± 0.36 μg/kg). Among patients with positive PCA, a higher dose of daily L-T4 was reported in those with proven gastritis in comparison to those without gastric damage (1.52 ± 0.40 μg/kg vs. 1.15 ± 0.33 μg/kg) ($P<0.0001$) (48).

Five patients with autoimmune gastritis, and hypothyroidism, were evaluated in a case series. Patients received L-T4 tablets, and upon the switch to the same dosage of liquid L-T4, circulating TSH normalized in all patients. Among them, four patients were switched back to L-T4 tablets at the same dosage, and TSH worsened again. It was concluded that liquid L-T4 can bypass the altered gastric pH associated with atrophic gastritis (49).

The proton pump inhibitors (PPIs) bind covalently to the H^+/K^+ATPase enzyme and this can block the secretion of gastric acid (50). A prospective cohort study was conducted in 24 patients, in whom L-T4 therapy failed after L-T4 and PPIs concurrent assumption. Following the switch from L-T4 tablets to the liquid formulation, at the same daily dose, a significant decrease in serum TSH was shown, even maintaining the co-ingestion of PPIs (51).

Intestinal Malabsorption

Drug malabsorption can derive from bariatric surgery (52, 53). A study evaluated 17 hypothyroid patients [who had received L-T4 tablets for >1 year prior surgery; four biliary pancreatic diversions (BPD); 13 Roux-en-Y gastric bypasses (RYGB)] with elevated TSH levels from 3 to 8 months after surgery. TSH significantly decreased following the switch from tablets to liquid L-T4 (30 min before breakfast, at the same dose), in patients submitted to RYGB, or BPD, in this way circumventing the issue of malabsorption in BPD-treated patients, and confirming preceding findings obtained in patients undergone to RYGB (52). Another study (53) reported four hypothyroid patients who were in euthyroidism with L-T4 tablets before RYGB, and whose TSH levels increased after surgery. Switching from tablets to the liquid formulation, TSH declined. These data permit to hypothesize that liquid L-T4 can bypass the malabsorption linked to bariatric surgery (52, 53).

Among the gastrointestinal diseases that lead to L-T4 malabsorption, lactose intolerance (LI) is of great interest. In case of LI, a low lactose diet should be used, such as a lactose-free L-T4 preparation, in order to re-establish euthyroidism, without increasing the necessary dose of L-T4 (54, 55).

A cohort study analyzed the necessary L-T4 dosage in 34 hypothyroid subjects with LI, but not compliant with a lactose-free diet (56). The target TSH was attained with a median L-T4 of 1.31 μg/kg/day in hypothyroid patients. In subjects with LI, 5/34 reached the desired TSH with 1.29 μg/kg/day L-T4 (a similar dose), whereas 29/34 needed a gradually augmented L-T4 dosage and the target TSH was achieved at a median L-T4 of 1.81 μg/kg/day ($P<0.0001$). Among them, six patients had also other gastrointestinal disorders, and needed L-T4 at the dose of 2.04 μg/kg/day. In the other 23 patients with isolated LI, a median L-T4 dosage of 1.72 μg/kg/day ($P<0.0001$) was necessary to achieve target TSH levels. These data showed that in presence of LI the necessity for oral L-T4 in hypothyroid patients increased significantly (56).

Moreover, in 5 patients with hypothyroidism and LI, the switch from L-T4 tablets with lactose to a liquid preparation without lactose at the same dose normalized serum TSH values (57). In the 1st patient, after 1 month from the switch to liquid L-T4, TSH was in the normal range, and it increased again with the re-administration of L-T4 tablets at the same dosage for 4 weeks. In the 2nd patient, the TSH level was elevated with L-T4 tablets 150 μg daily, and upon 1 month from the switch to the liquid formulation it was in the normal range. To investigate the relationship between TSH

normalization and the oral preparation, L-T4 tablets was re-administered for 4 weeks at the same dose, and circulating TSH worsened again. In the 3rd patient, the L-T4 dose was increased, with no correction of hypothyroidism. Then the patient was switched to a liquid formulation and TSH was in the normal range after 1 month. Once L-T4 tablets were re-administered for 4 weeks, serum TSH increased again. The 4th patient received L-T4 tablets after thyroidectomy for PTC and radioiodine treatment. Owing to LI, the dose of L-T4 was augmented but hypothyroidism was not corrected. The patient was switched to liquid L-T4 at the same dose, and TSH values normalized. Following 2 months, TSH was suppressed, and it was maintained suppressed through time. The 5th patient, with autoimmune thyroiditis and hypothyroidism, was switched to liquid L-T4, owing to LI, and upon 2 months, TSH levels were in the normal range. The reported data demonstrated that the liquid L-T4 preparation permitted a better control of TSH, and when TSH, FT3, FT4 were measured again after 6 months, still resulted in the normal range in all the 5 cases (57).

Celiac disease (CD) is another important cause of L-T4 malabsorption. It is an immune-mediated enteropathy, caused by the ingestion of wheat gluten in genetically predisposed subjects (58). A gluten-free diet can improve TSH levels in patients with CD, indicating the importance of the impairment of the intestinal barrier in this disease. A study evaluated the necessary L-T4 dose in 35 patients with hypothyroidism, chronic autoimmune thyroiditis and atypical CD, reporting the need of an increased dose of L-T4, reversed by a gluten-free diet or by increasing T4 dose (59).

Five hundred hypothyroid patients were enrolled in a study and 144/500 needed a L-T4 dose ≥125 μg/day. Nine patients had CD, and 8/9 needed ≥125 μg/day of L-T4. Patients requiring ≥125 μg/day of L-T4 had a significantly higher risk of CD ($P<0.001$), and CD was found in 5.6% of them (60).

Patients With No Malabsorption or Drug Interference

The effectiveness of liquid L-T4 was evaluated in hypothyroid patients with no malabsorption or drug interference.

A prospective study enrolled 152 hypothyroid subjects with no malabsorption or drug interference, switched from tablets to liquid L-T4, 30 min before breakfast, at the same dose (61). TSH values significantly declined at the 1st ($P<0.05$) and the 2nd control ($P<0.01$), whereas FT4 and FT3 did not change, suggesting a higher effectiveness of liquid L-T4 (than tablets) to control TSH in hypothyroid subjects with no malabsorption, drug interference, or gastric disorders (61).

Moreover, a study enrolled after thyroidectomy 105 patients without malabsorption, of whom 52 received liquid L-T4, and 53 L-T4 tablets, with the same dose (1.5 μg/kg/day) (62). The day after surgery, patients began to take the medication, 30 min before breakfast. Significantly lower TSH values were obtained in patients receiving liquid L-T4, in comparison to those administered with the tablets, at the 1st ($P<0.05$), and the 2nd control ($P<0.01$), whereas FT4 and FT3 did not change. Patients treated with L-T4 tablets were more prevalently in the hypothyroid range of TSH (>3.6 μU/ml) (62).

Another study was conducted in 21 hypothyroid subjects with no malabsorption or drug interference, with elevated TSH levels under therapy with L-T4 tablets. Patients were switched to the liquid formulation at the same dose, 30 min before breakfast, and TSH significantly decreased 2 months following the switch (63). Among the 21 patients, 15 switched back to tablets, and TSH raised again to hypothyroid values. All subjects were then administered with the liquid L-T4, and TSH, FT3, and FT4 were measured again following 6 and 12 months, and resulted in the normal range (63). It was concluded that in hypothyroid patients with no malabsorption, drug interference, or gastric disorders, the liquid formulation is better in the control of TSH levels with respect to tablets (62, 63).

The prevalence of aberrant thyroid function has been controversial for a long time. A study evaluated the prevalence of elevated TSH in participants in a statewide fair in Colorado. The prevalence of high values of TSH was 9.5% and of decreased TSH levels of 2.2%. The findings reported that 40% of patients taking thyroid medications had abnormal TSH values (37).

Furthermore, another study evaluated patients treated for differentiated thyroid cancer (DTC), randomly administered with L-T4 in tablets or in liquid solution (36). One hundred and two patients were enrolled, 51 treated with L-T4 tablets and 51 with the liquid formulation, at the dose of 1.9 μg/kg/day, from the day after post-surgery ^{131}I treatment. The 1st control was done 8–12 months after ^{131}I remnant ablation, and furtherly after 12 months. TSH increased significantly in patients taking tablets in comparison to those receiving the liquid preparation. The authors concluded that liquid L-T4 can lead to a significantly more elevated number of DTC patients with TSH levels in range for the American Thyroid Association (ATA) risk score, decreasing TSH variability through time (36).

More recently, a study compared the stability of TSH in hypothyroid patients taking liquid L-T4 compared to those receiving tablets (64). Five hundred and fifty hypothyroid patients received the liquid formulation, and 225 L-T4 tablets. After 1 year, normal TSH levels were present in 91% of the patients who received the L-T4 liquid solution whereas only in 85% of those taking L-T4 tablets. After 2 years, TSH normal values were attained in 87% of patients who received the L-T4 liquid preparation while only in 76% of those administered with tablets ($P<0.05$) (64).

CONCLUSION

The frequency of hypothyroidism is higher in women, especially over 60 years. It is present in about 5% of the population and it can be diagnosed measuring serum TSH and free T4 values. After the diagnosis of hypothyroidism the usual therapy is tablet L-T4, monitoring TSH values in primary hypothyroidism every 6–8 weeks. Once the TSH is stabilized in the normal range, it is recommended to conduct annual testing on all treated subjects to warrant suitable replacement.

L-T4 absorption can be impaired by various conditions, such as with some food, or assuming it during breakfast, or

conditions of reduced gastric acidity, bariatric surgery, LI, CD, and drugs that alter the gastric pH, avoiding the dissolution of tablets.

New oral L-T4 formulations have been developed: the liquid preparation, and soft gel capsule. The liquid solution does not require an acid gastric environment, and soft gel capsule permits a quick dissolution in the acid gastric pH, demonstrating a more rapid absorption for liquid L-T4, or capsule, than tablets.

Liquid L-T4 Should Be Used Right From the Start of the Treatment in the Following Categories of Hypothyroid Patients:

- with food and beverages (coffee, etc.) interference with tablet L-T4 absorption and not compliant with the abitual ingestion of L-T4 30–60 min before breakfast;
- with malabsorption associated with an increased gastric pH;
- with malabsorption after bariatric surgery, or with intestinal malabsorption;
- with malabsorption induced by interferent drugs;
- with typical or atypical CD, or in patients with LI;
- who are not able to swallow the tablets.

Furthermore, liquid L-T4 should be used in patients with a sub-optimal response to tablets L-T4, and a TSH threshold of >4 μU/ml should be used for switching to the liquid formulation.

Moreover, many studies have suggested that liquid L-T4 permits to maintain more efficiently normal TSH in hypothyroid patients in the long term follow-up, than L-T4 tablets, both in patients with malabsorptive states, than in those without malabsorption.

Further large, prospective, longitudinal studies are necessary to evaluate the stability of TSH, in hypothyroid patients administered with different L-T4 formulations.

AUTHOR CONTRIBUTIONS

AA, SMF, and PF conceived the paper. All authors contributed to the article and approved the submitted version.

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Abnormal Brain Glucose Metabolism in Papillary Thyroid Cancer Patients 4 Weeks After Withdrawal of Levothyroxine: A Cross-Sectional Study Using ^{18}F-FDG PET/CT

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Wu S-q, Feng F, Zou R-j, Fu H-l, Sun J-w, Jia X-z, Yin Y-f and Wang H (2021) Abnormal Brain Glucose Metabolism in Papillary Thyroid Cancer Patients 4 Weeks After Withdrawal of Levothyroxine: A Cross-Sectional Study Using ^{18}F-FDG PET/CT. Front. Endocrinol. 12:595933. doi: 10.3389/fendo.2021.595933

Background: There is no doubt that thyroid dysfunction is associated with psychiatric disorders. A large amount of thyroid carcinoma patients displayed mood disorders after the withdrawal of levothyroxine (LT4). However, it is unclear whether the disorders are related to the transient withdrawal of LT4, and if yes, what the possible underlying mechanism is. This study aims to investigate the abnormal regional cerebral glucose metabolism (rCMRglu) in a group of papillary thyroid cancer (PTC) patients without LT4 for 4 weeks and prove the relationship between the abnormal rCMRglu with depression and anxiety.

Methods: Brain ^{18}F-FDG PET/CT data of 38 consecutive PTC patients with high/intermediate-risk from June 2016 to December 2017 have been analyzed. Of the 38 patients, 23 are in the LT4 withdrawal group (WG) and 15 in the LT4 replacement group (RG). These patients were also evaluated for depressive and anxiety symptoms within 24 h after the scans based on the Hamilton Depression Rating Scale (17 items, HRDS-17) and the Hamilton Anxiety Rating Scale (HAMA) respectively.

Results: Thirty-eight patients (12 men, 26 women; age range, 25–69 years; mean age, 45.8 years) were selected in the study. Compared with the RG, patients in WG showed depression and anxiety with higher total scores of HRDS-17 and HAMA (14.7 ± 5.8 *vs* 3.8 ± 5.5, t = –5.74, p = 0.00; 9.3 ± 4.3 *vs* 2.7 ± 4.1, t = –4.74, p = 0.00, respectively). In the brain glucose metabolism analysis, the WG patients showed lower rCMRglu in Occipital_Mid_R and Postcentral_L. On the other hand, data illustrated significant rCMRglu increases in the Frontal_Sup_Orb_L. Compared with the healthy group (HG), the rCMRglu of the Postcentral_L and Precuneus_L showed hypoactivity, but the Hippocampus_R and the Temporal_Inf_L showed hyperactivity. This analysis yielded a

significant correlation between abnormal rCMRglu with the free thyroxine level, the serum thyroid-stimulating hormone level, HRDS-17, and HAMA scores.

Conclusions: The findings showed that more PTC patients exhibited depression and anxiety after LT4 withdrawal for 4 weeks. More attention should be paid to these hypothyroid patients while they were in the hospital. Such a short-term LT4 withdrawal also likely induced abnormal rCMRglu. Our study attempts to explain the possible mechanism of mood disorders related to transient hypothyroidism.

Keywords: papillary thyroid carcinoma, regional cerebral glucose metabolism, hypothyroidism, mood disorders, PET/CT

INTRODUCTION

The association between thyroid function and psychiatric disorders was described more than 200 years ago (1). Overt hypothyroidism is a major cause of mood disorder (2). Even subclinical hypothyroidism was connected with depression, especially in young patients (3). Early studies observed abnormal regional cerebral glucose metabolism (rCMRglu) or cerebral blood flow (CBF) in patients under hypothyroidism (4–7). However, only a few studies focused on rCMRglu in thyroid carcinoma (TC) patients under transient hypothyroidism (8).

With the rapid increase of thyroid cancer and the unavailability of recombinant human thyrotropin (rhTSH) and triiodothyronine (T3) in mainland China, the experts of the Chinese Society of Nuclear Medicine (CSNM) typically recommends a short-time withdrawal from thyroid hormone (levothyroxine, Euthyrox, Levothyroxine Sodium, Merck Sdn Bhd, Germany) for post-treatment assessment or preparing for the iodine 131 (^{131}I) ablation of TC patients in clinical practices (9). Consequently, we observed a significant amount of patients began to suffer mood disorders. With advances in brain imaging technology, a combination of endocrine and psychological testing as well as PET scan can provide insight into the underlying mechanisms of the functional neuroendocrine relationships (10). Therefore, the authors attempt to apply similar technics to study the relationship between hypothyroid-related mood disorder and abnormal rCMRglu in transient hypothyroidism papillary thyroid carcinoma (PTC) patients.

To the authors' knowledge, this is the first clinical PET/CT study comparing the glucose metabolism of the brain in age, gender, education, body mass index (BMI), pTNM stage, and risk category-matched PTC patients with or without thyroid hormones for 4 weeks in mainland China. We performed this cross-sectional study to investigate whether 4 weeks of transient hypothyroidism by LT4 withdrawal could cause mood disorders and changes in rCMRglu on PET/CT.

MATERIALS AND METHODS

Subjects

This retrospective study was approved by the Ethics Committee of Xin Hua Hospital Affiliated to Shanghai Jiaotong University School of Medicine (Approval No. XHEC-D-2019-117). Informed consent was obtained for all the patients/healthy participants for the publication of any potentially identifiable images, or data included in this article. From June 2016 to December 2017, 38 pathology-proofed PTC patients (12 men, 26 women; age range, 25–69 years; mean age, 45.8 years) who were standardly performed brain ^{18}F-FDG PET/CT were analyzed in the study (**Figure 1**). Among them, 23 were in the LT4 withdrawal group (WG) and 15 in the LT4 replacement group (RG).

The inclusion criteria are: 1) all patients received total thyroidectomy, and the histological results were PTC; 2) Standard brain 18F-FDG PET/CT was performed in selected patients with high/intermediate-risk according to the guidelines of the American Thyroid Association (11) under standardized conditions described in the study; 3) HRDS-17 and HAMA questionnaires were evaluated within 24 h and thyroid function testing was performed within 3 days after the scans; 4) no known history of other endocrine problems and other malignant tumor diseases; 5) brain CT or MRI was performed for all patients to affirm no previous trauma or surgery of the brain.

The exclusion criteria are: 1) any history of alcohol or drug dependence; 2) medical records with diagnoses of psychiatric disorders and/or related medications; 3) severe medical conditions, such as organic brain disorders and neurological diseases including cerebrovascular diseases and seizures; 4) histories of head trauma; 5) serious somatic illnesses; 6) current pregnancy or breastfeeding.

We enrolled another 34 healthy subjects (7 men, 27 women; age range, 27–82 years; mean age, 48.97 years) from the same period as a healthy group (HG), following the 1:1 pairing rule for age and sex factors. The HG subjects were in euthyroid status during the sampling period and have given their written consents for participation in this study.

All of the selected PTC and healthy subjects were born in mainland China and of Chinese Han ethnicity. All were right-handed.

Clinical Assessment

We recorded clinical information for each subject, including gender, body weight, height, years of education and career, pTNM stage, risk category, and thyroglobulin and thyroglobulin antibody levels. BMI was calculated. Serum levels of triiodothyronine (T3), free triiodothyronine (FT3), thyroxine (T4), free thyroxine (FT4), and TSH were also measured in blood samples using a time-resolved immunofluorometric assay

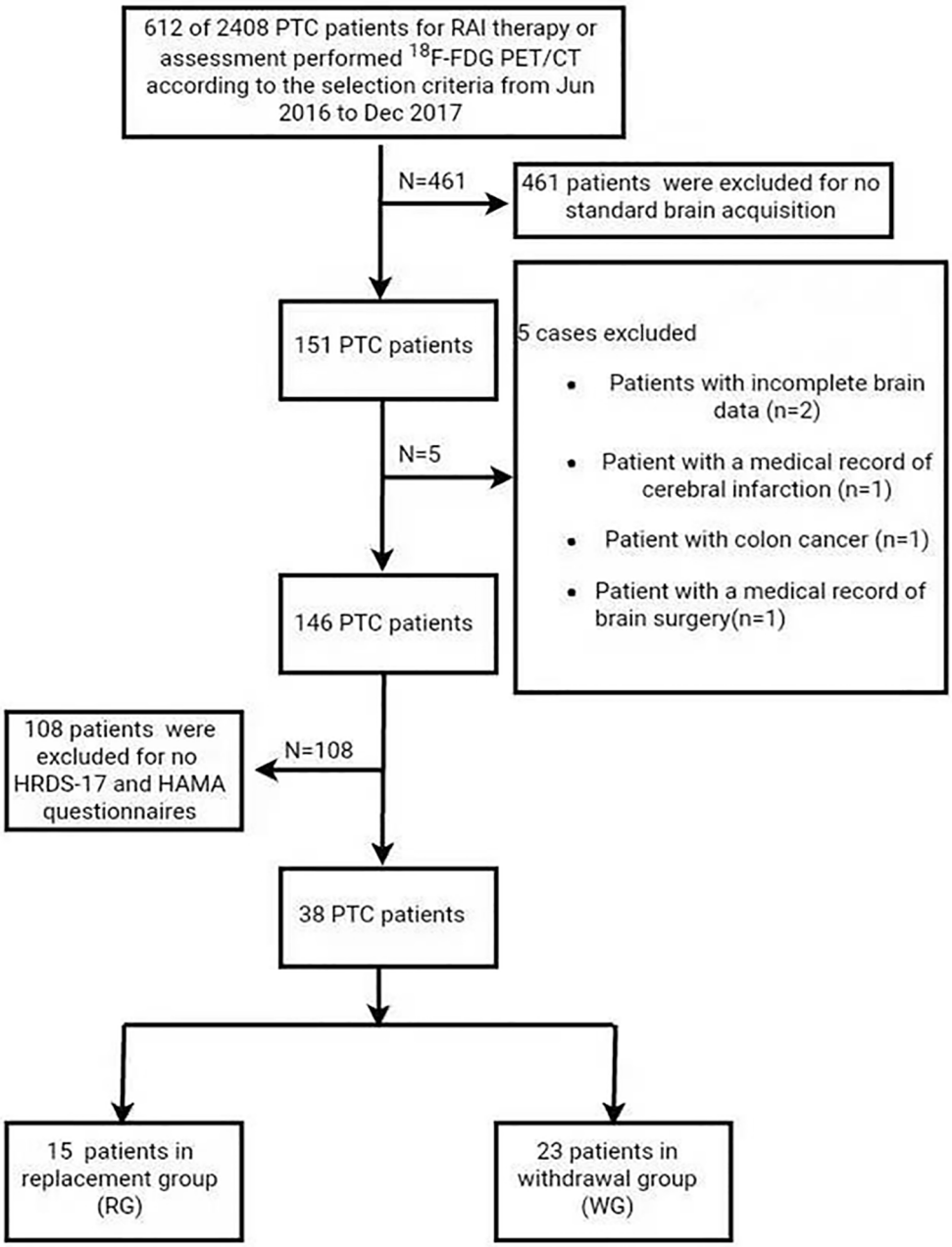

FIGURE 1 | Flow chart of patients included in the current study. PTC, papillary thyroid carcinoma.

(Any test, Sym-Bio Life Science Co., Ltd., Shanghai, China). Both HRDS-17 and HAMA tables, which were validated for use in mainland China (12, 13), were printed in Chinese and evaluated by a trained doctor who was blinded to the patients' information. All subjects completed the scale assessments satisfactorily. The total HRDS-17 score has a range from 0 to 68, with a score higher than 17 reflecting moderate/severe depressed status (12–14). The HAMA value is used for assessing anxiety symptoms. The total score has a range from 0 to 64, with a score higher than 7 indicating increased anxiety (13).

Brain ^{18}F-FDG PET/CT Image Acquisition

^{18}F-FDG PET/CT was performed on all subjects using a PET/CT scanner (Biograph mCT64, Siemens Medical Systems, Knoxville, TN, USA) in the 3D mode 45 min after intravenous injection of FDG (5.55 MBq/kg). Each patient was asked to fast for at least 6 h to ensure a serum glucose concentration of less than 150 mg/dl. After the injection, the subjects rested lying in a quiet, dimly lit environment. He or she was then evaluated with arms down and eyes closed in a dark and quiet examination room. The PET scan lasted for 10 min for each subject. A CT transmission scan

was first obtained for attenuation correction (X-ray tube tension of 120 kV, current of 100–250 mAs, rotation time 0.8 s, and slice thickness 3 mm). Hanning filters and TureX (HD-PET) were used during image reconstruction. We used normalized count images to measure relative changes in regional glucose metabolism.

Data Processing

Preprocessing of PET data was performed using the statistical parametric mapping 5 (SPM5, the Wellcome Department of Neurology, London U.K.) in MATLAB R2006a (MathWorks Inc., Sherborn, MA, USA). The PET images were spatially normalized to the SPM PET template (Montreal Neurological Institute, McGill University, Montreal, Canada), resliced with a voxel size of $2 \times 2 \times 2$ mm^3, and smoothed with a 10 mm full-width half-maximum isotropic Gaussian kernel. For standardization purposes, each voxel in the PET image was then divided by the global mean value of each individual (15).

Statistical Analysis

To compare the PET maps between WG with RG and WG with HG respectively, two-sample t-tests were performed to identify the regions with significant differences with adjustments for age and sex. The statistical threshold was set at a threshold of individual voxel $p < 0.005$ at the voxel level and clusters size >150 voxels. The Pearson correlation analysis was performed with clinical/physiological/biochemical characteristics of the patients (including TSH, FT3, FT4 levels, the score of the HRDS-17 and HAMA) while adjusting for age and sex. The correlations were considered significant at a threshold of individual voxel $p < 0.005$, clusters size >150 voxels. The analyses were performed using RESTplus (16).

Differences in demographic and clinical variables between different groups were examined with independent t-test and chi-square test for sex. Fisher`s exact test for stage and risk category. A p value <0.05 (two-tailed) was considered statistically significant. All statistical analyses were conducted with SPSS software, version 22.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Clinical Features

Thirty-eight consecutive patients with papillary thyroid carcinoma confirmed by pathology after total thyroidectomy were recruited in the study. Tumor staging was defined according to AJCC TNM, seventh edition (11); 18 patients were in stage I, 12 patients were in stage III, and 8 patients were in stage IV. Initial American Thyroid Association (ATA) risk stratification indicated intermediate-risk in 27/38 of the patients (71.1%) and high-risk in 11/38 of the patients (28.9%) based on clinical risk stratification for thyroid cancer. The demographic and clinical characteristics of the participants were presented in **Table 1**. There was no significant difference in age ($p = 0.31$), sex ratio ($p = 0.37$), years of education ($p = 0.86$), and BMI ($p = 0.15$) between the two groups. The pTNM stage and risk category were also compared using Fisher`s exact test ($p = 0.35$ and 0.07, respectively). There was no significant difference in Tg and TgAb ($p = 0.25$ and 0.09, respectively). As all the patients in the WG had clinically diagnosed hypothyroidism, the serum levels of T3 ($t = -10.36$, $p = 0.00$), T4 ($t = -18.25$, $p = 0.00$), FT3 ($t = -5.66$, $p = 0.00$), and FT4 ($t = -17.62$, $p = 0.00$) were lower than those in the RG, whereas the TSH level ($t = 11.98$, $p = 0.00$) was higher.

Table 2 shows the primary clinical information of the WG and HG. The mean age in the HG was higher than that in the WG, but there was no statistically significant difference (49.0 *vs.* 44.1, $t = 1.4$, $p = 0.17$). Moreover, the sex ratio in the two groups was not significantly different.

TABLE 1 | Demographic and clinical characteristics of the study participants.

	RG (n = 15)	WG (n = 23)	Test[a]
Age, year	48.3 ± 13.3	44.1 ± 11.3	t = –1.03, p = 0.31
Gender (male/female)	6/9	6/17	χ^2 = 0.81, p = 0.37
Education, year	11.3 ± 3.9	11.0 ± 4.7	t = –0.18, p = 0.86
BMI	25.8 ± 3.7	24.0 ± 3.6	t = –1.47, p = 0.15
HRDS-17	3.8 ± 5.5	14.7 ± 5.8	t = –5.74, p = 0.00
HAMA	2.7 ± 4.1	9.3 ± 4.3	t = –4.74, p = 0.00
pTNM stage (I/III/IV)	6/4/5	12/8/3	p = 0.35[b]
Risk category (high/intermediate-risk)	7/8	4/19	p = 0.07[b]
T3, nmol/L (range[c])	1.1 ± 0.2 (1.0–1.2)	0.3 ± 0.3 (0.2–0.4)	t = –10.36, p = 0.00
T4, ng/ml (range)	109.2 ± 14.0 (84.7–140.3)	14.5 ± 16.60 (0.01–71.4)	t = –18.25, p = 0.00
FT3, pmol/L (range)	4.1 ± 0.9 (3.3–7.0)	2.2 ± 1.1 (0.1–4.0)	t = –5.66, p = 0.00
FT4, pmol/L (range)	18.1 ± 3.4 (14.2–25.7)	1.8 ± 2.3 (0.01–9.0)	t = –17.62, p = 0.00
TSH, uIU/ml (range)	0.5 ± 0.6 (0.01–2.04)	123.0 ± 49.0 (39.68–172.5)	t = 11.98, p = 0.00
Tg, ng/ml (range)	7.1 ± 8.5 (0.1–28.9)	16.3 ± 19.5 (0.1–83.8)	t = 1.17, p = 0.25
TgAb, IU/ml (range)	10.8 ± 4.7 (1.0–18.2)	8.3 ± 8.2 (1.3–42.0)	t = 1.72, p = 0.09

[a]*Independent t-test for continuous variables and chi-square test for sex.*

[b]*Fisher's exact test.*

[c]*range: from minimum to maximum.*

RG, levothyroxine replacement group; WG, levothyroxine withdrawal group; BMI, body mass index; HRDS-17, 17 items of Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; Tg, thyroglobulin; TgAb, thyroglobulin antibody.

TABLE 2 | The clinical information of HG and WG.

	HG (n = 34)	WG (n = 23)	Test
Age, year	49.0 ± 13.7	44.1 ± 11.3	t = 1.40, p = 0.17
Gender (Male/female)	7/27	6/17	χ^2 = 0.24, p = 0.63
Education, year	11.0 ± 3.3	11.0 ± 4.7	t = 0.00, p = 1.00
BMI	22.9 ± 2.6	24.0 ± 3.6	t = −1.29, p = 0.20

Independent t-test for continuous variables and chi-square test for gender.

HRDS-17 and HAMA Values in the WG and RG

The total scores of HRDS-17 were 14.7 ± 5.8 in the WG and 3.8 ± 5.5 in the RG, with a significant difference between the two groups (t = −5.74, p = 0.00). Seven of 23 (30.4%) subjects in the WG were in a depressive state while only 1/15 (6.7%) patients in the RG had depressive status (HRDS-17 score 23). For the HAMA total score, the statistical result was also significant (9.3 ± 4.3 in the WG and 2.7 ± 4.1 in the RG, t = −4.74, p = 0.00) (**Table 1**). A total of 16/23 (69.6%) patients showed anxiety in the WG, while only one of those patients showed anxiety in the RG, with a score of 16.

LT4 Withdrawal-Related Different Changes in Relative Cerebral Glucose Metabolism: WG Compared With RG/HG, Respectively

Compared with the RG, patients in the WG showed significantly decreased ^{18}F-FDG uptake in the right middle occipital gyrus (Occipital_Mid_R, MOG.R) and the left postcentral gyrus (Postcentral_L, PoCG.L) (uncorrected P < 0.005, cluster sizes >150; **Table 3** and **Figure 2**). The rCMRglu significantly increased in the left superior frontal gyrus, orbital part (Frontal_Sup_Orb_L, ORBsup.L).

Compared with the HG, patients in the WG showed hyperactivity in the right hippocampus and the left inferior temporal gyrus (Temporal_Inf_L, ITG.L). In contrast, the rCMRglu demonstrated decreased metabolism in the left postcentral gyrus (Postcentral_L, PoCG.L) and left precuneus (Precuneus_L, PCUN.L) (uncorrected p < 0.005, cluster sizes >150; **Table 3** and **Figure 3**).

Correlations of Thyroid Function (TSH, FT3, and FT4), Depressive (HRDS-17) and Anxious (HAMA) Symptoms With Relative Cerebral Glucose Metabolism in the WG

Table 4 illustrates the correlations of thyroid function status, depression, and anxiety scores with relative rCMRglu in the WG. The correlation analysis shows a significantly positive correlation between the glucose metabolic activity in both the left superior frontal gyrus, medial (Frontal_sup_Medial_L, SFGmed.L) and the right supplementary motor area (Supp_Motor_Area_R, SMA.R) with the FT4 level (**Figure 4B**). But no significant correlations can be found between the free triiodothyronine (FT3) level with the glucose metabolic activity in any other gyrus. A negative correlation was found between the serum TSH level and the left rolandic operculum (Rolandic_Oper_L, ROL.L) and the right Heschel gyrus (HES.R), while the right parahippocampal gyrus (ParaHippocampal_R, PHG.R) was positively correlated to the serum TSH level (**Figure 4A**). The glucose metabolism of the left gyrus rectus (Rectus_L, REC.L) was positively correlated to HRDS-17 scores (**Figure 4C**). And the HAMA score was positively correlated to the metabolic activity of the left fusiform gyrus (Fusiform_L, FFG.L), the left middle temporal gyrus (Temproral_Mid_L, MTG.L), and the right gyrus rectus (Rectus_R, REC.R) (**Figure 4D**).

DISCUSSION

This study mainly observed that even 4 weeks of LT4 withdrawal could lead to mood disorders and several brain regions of abnormal

TABLE 3 | Brain Areas Showing Different rCMRglu between WG with RG or HG, separately.

Brain region	Side	Cluster size (voxels)	Coordinate (x, y, z)	Peak T-Value
WG vs RG				
Occipital_Mid	R	192	36 −84 20	−4.18
Postcentral	L	165	−48 −30 50	−4.41
Frontal_Sup_Orb	L	160	−14 14 −18	4.00
WG vs HG				
Postcentral	L	248	−48 −30 50	−3.98
Precuneus	L	255	−4 −64 64	−4.32
Temporal_Inf	L	271	−48 0 −46	3.96
Hippocampus	R	326	28 −32 −8	4.42

Results were uncollected at a p-value <0.005 at the voxel level, for clusters k >150 voxels[a].

[a]WG, Levothyroxine withdrawal group; RG, Levothyroxine replacement group; HG, healthy control group.

The coordinates refer to the Montreal Neurological Institute (MNI) coordinate system; L, left; R, right.

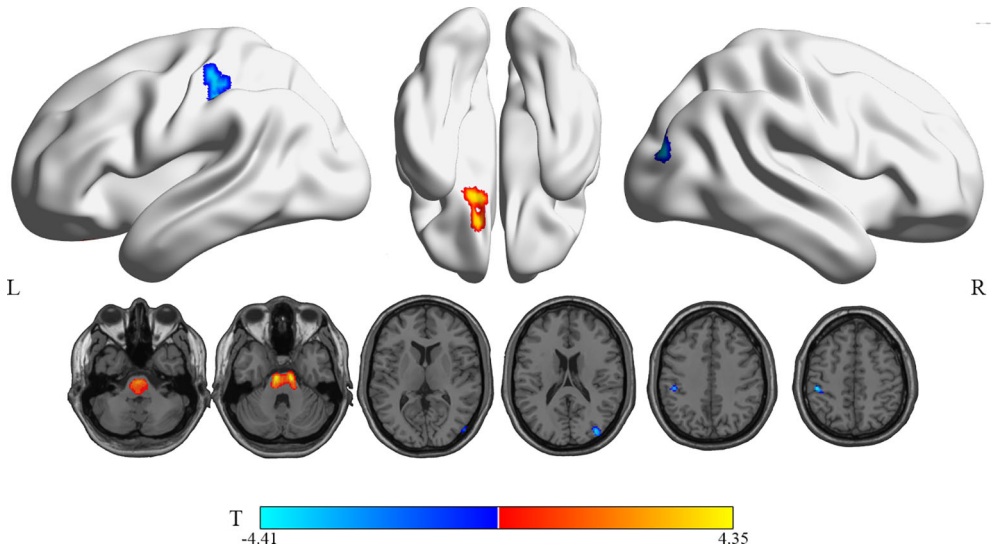

FIGURE 2 | Brain regions with significant rCMRglu differences in WG compared with RG subjects. Compared with RG, glucose metabolism in WG patients decreased (cool) in the occipital_Mid_R and postcentral_L, but increased (warm) in the Frontal_Sup_Orb_L(uncorrected p-value <0.005; extend threshold = 150). The figure is depicted in neurologic orientation. The 3D render view and gray-scale image (a T1 structural MR image that is representative of MNI space). The color bar represents the T-value for each voxel.

glucose metabolisms in PTC patients in China. Firstly, we observed patients in the WG with higher HRDS-17 and HAMA total scores, meant even transient hypothyroidism caused depression and anxiety. Secondly, the brain glucose metabolism of WG was compared with RG and HG, respectively. The results indicated that patients in the WG exhibited significantly decreased rCMRglu in the right occipital and the left postcentral gyrus, while increased in the left frontal gyrus. When compared with HG, in addition to the left posterior central gyrus, the glucose metabolism of the left precuneus was decreased, and the metabolism of the left temporal gyrus and the right parahippocampal gyrus increased. Thirdly, we identified some special regions in the WG that were related to the thyroid function (TSH and FT4) and depressive (HRDS-17)/anxious (HAMA) symptoms. This study confirmed that even after 4 weeks of LT4 discontinuation, the patients were at risk of neuropsychiatric disturbances. And several brain regions were affected by the thyroid dysfunction. Therefore, the regions had possible correlations with the transient thyroid dysfunction and mood disorders in this study.

Firstly, this study indicated that even temporary hypothyroidism could cause abnormal mood status in PTC patients. In clinical, we observed patients in the WG with higher HRDS-17 and HAMA scores. The results consisted with most studies, which reported that thyroid dysfunction indeed caused depressive and anxiety symptoms (4, 17–21). Therefore, this study has reconfirmed that hypothyroidism, even for a short duration, can cause abnormal mood swings and lead to increased risks of severe disorders such as depression and anxiety. Based on our conclusion, we recommend that neuropsychiatric tests including cognitive functions be used in patient management practices especially when LT4 withdrawal is involved.

Further, the brain glucose metabolism of the patients in WG was compared with RG/HG, respectively (**Table 3** and **Figures 2** and **3**). It is worth pointing out that several brain regions in which PTC patients with transient thyroid dysfunction reliably exhibited hypo/hypermetabolic compared with RG and healthy controls.

1. The decreases of rCMRglu in the MOG.R/PoCG.L (WG *vs* RG) and the PCUN.L/PoCG.L (WG *vs* HG) found in this study are generally in line with the previous neuroimaging studies carried out on hypothyroid patients. Decreased patterns of brain metabolism or CBF parietal-occipital areas, including postcentral gyrus, have been discussed (4, 5, 7, 19, 22). When compared with HG, another finding was the precuneus, an important role in the default mode network (DMN). Raichle demonstrated the DMN had high levels of metabolic activity during wakefulness, including the cingulate, precuneus, and parietal regions (15). According to our findings, among PTC patients with hypothyroidism, even for a short time, the left precuneus (important seed in DMN) showed lower rCMRglu. Therefore, the right occipital gyrus, the postcentral gyrus, and the DMN (especially the precuneus) may be cores of the potential target of these transient hypothyroidism-related mood disorders in hypothyroid PTC patients.

2. The hypermetabolism found in this study related to the ORBsup.L (WG *vs* RG) and the right hippocampus/the ITG.L (WG *vs* HG) seem to be special regions in transient hypothyroidism. The ORBsup.L is activated by both pleasant and unpleasant words and is associated with the posterior cingulate cortex. That means the importance of ORBsup.L in normal emotional processing, participating in clearly emotional/motivational executive functions (23, 24). Besides, we found

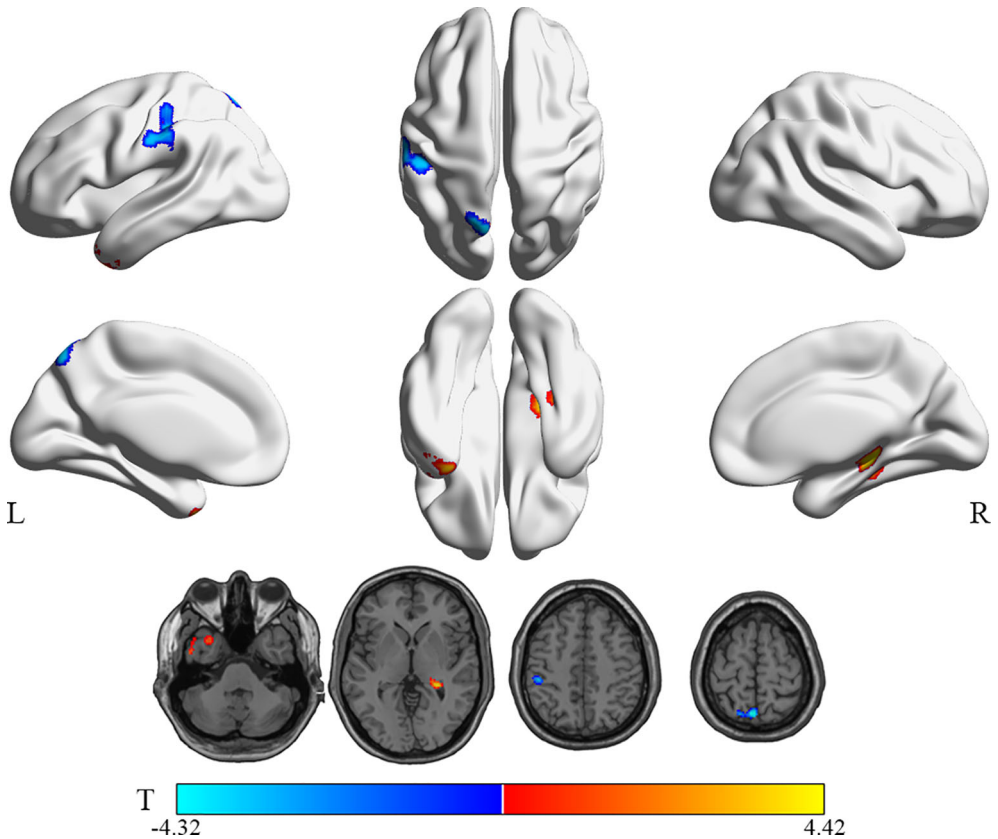

FIGURE 3 | Brain regions with significant rCMRglu differences in WG compared with HG subjects. Compared with HG, glucose metabolism in WG patients decreased (cool) in the precuneus_L and postcentral_L, but increased (warm) in the Temporal_Inf_L and Hippocampus_R (uncorrected p-value <0.005; extend threshold = 150). The color bar represents the T-value for each voxel.

TABLE 4 | The correlation of thyroid function (TSH, FT3, and FT4), depressive (HRDS-17) and anxious (HAMA) symptoms with relative cerebral glucose metabolism in the WG.

Brain region	Side	Cluster size (voxels)	Coordinate (x, y, z)	Peak R-Value
TSH				
ParaHippocampal	R	188	22, 6, –26	0.69
Rolandic_Oper	L	372	–36, –28, 16	–0.80
Heschel	R	156	38, –26, 14	–0.68
FT3				
N/A	N/A	N/A	N/A	N/A
FT4				
Frontal_Sup_Media	L	483	–2 38 32	0.81
Supp_Motor_Area	R	215	4, 5, 60	0.67
HRDS-17				
Rectus	L	566	–2, 34, –26	0.71
HAMA				
Fusiform	L	318	–32, –14, –28	0.71
Temproral_Mid	L	158	–56, –8, –20	0.74
Rectus	R	399	4, 30, –18	0.72

Results were uncollected at a p-value <0.005 at the voxel level, for clusters k >150 voxels[a].

[a]WG, Levothyroxine withdrawal group.

The coordinates refer to the Montreal Neurological Institute (MNI) coordinate system; L, left; R, right; HRDS-17, 17 items of Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; FT4, free thyroxine; TSH, thyroid-stimulating hormone; N/A, Not Applicable.

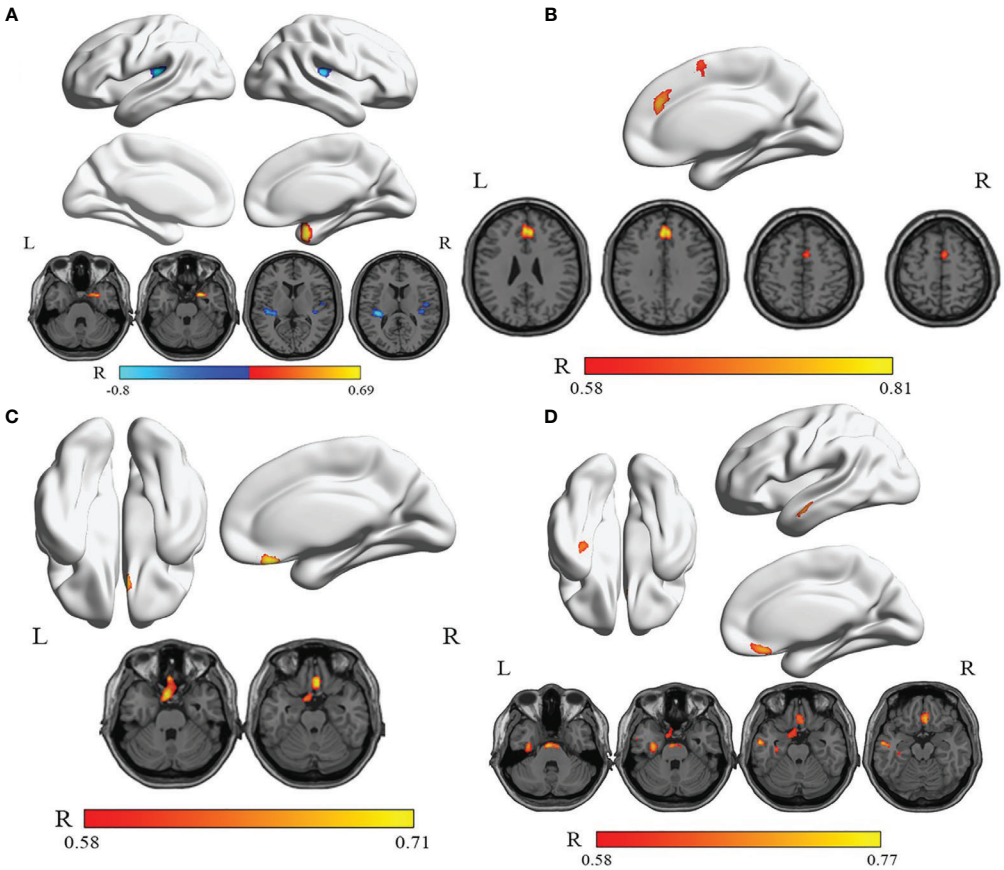

FIGURE 4 | The correlations between serum TSH, FT4 levels, HRDS-17, HAMA scores, and relative rCMRglu in WG. **(A)** The rCMRglu in the left rolandic operculum and the right Heschel gyrus (cool) was a negative correlation with the serum TSH level, while the right parahippocampal gyrus (warm) was positively correlated. **(B)** The rCMRglu of the left medial superior frontal gyrus and the right supplementary motor area (warm) had a positive correlation with the serum FT4 level. **(C)** The glucose metabolism of the left gyrus rectus was positively correlated to the HRDS-17 score (warm). **(D)** The rCMRglu of the left fusiform gyrus, the left middle temporal gyrus, and the right gyrus rectus were positively correlated to the HAMA score (warm). The color bar represents the R-value for each voxel.

increased metabolism in the right hippocampus and the left temporal gyrus in comparison with healthy controls, both of these regions may be related to anxiety (25, 26). An fMRI study identified reversible hypoperfusion in the anterior and posterior cingulate cortex, amygdala, and hippocampus in previously untreated hypothyroidism (27). Several brain regions were affected by thyroid dysfunction. We recommend that further studies on the relations between transient thyroid dysfunction and mood disorders continue to target these key regions.

Besides, we identified correlations between brain activities in certain cerebral regions, the thyroid functions (TSH and FT4), and the depressive (HRDS-17)/anxious (HAMA) symptoms in the WG. Multiple brain regions exhibited either positive or negative relationships. As we all know, thyroid hormones can regulate gene transcription through nuclear receptors, but the level of thyroid hormones in the brain cannot be measured. For example, Homan indicated that some key regions are sensitive to the low levels of hormones (28).

This study has limitations. Firstly, it was a cross-sectional study and therefore had a relatively small sample size. There are biases in PTC patients and healthy controls selection (six healthy subjects suffered from thyroiditis but in euthyroid status). Secondly, the connections in the whole brain are complex, and rCMRglu measures only one aspect of brain metabolisms. For example, if fMRI data were added, it could shed more light on the brain's response to transient thyroid dysfunctions. Thirdly, the dynamic relationship between the level of peripheral thyroid hormone and the level of the cerebrospinal fluid, which directly affects abnormalities in the brain, was not clear. Moreover, other factors such as the hypothalamus-pituitary-thyroid (HPT) axis can also cause mood disorders. For example, in another study by our team, it was common to find high physiological FDG uptake of the pituitary in DTC patients (29).

CONCLUSION

This is the first clinical study of the rCMRglu in age, gender, education, BMI, pTNM stage, and risk category-matched hypothyroidism DTC patients caused by the withdrawal of LT4

for 4 weeks in mainland China. In such hypothyroid status, patients showed depression and anxiety symptoms. We suggested more attention should be paid to these hypothyroid patients while they were in the hospital. Furthermore, such short time hypothyroidism may induce abnormal rCMRglu in the brain of DTC patients. Our findings may play a role in a deeper understanding of these transient hypothyroidism-related mood disorders. Of course, the current findings need to be further validated in a longitudinal study.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Xin Hua Hospital Affiliated to Shanghai Jiaotong University School of Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

S-qW, Y-fY, and HW designed the study. FF, H-lF, and R-jZ collected clinical data. J-wS and X-zJ conducted the statistical analysis. S-qW drafted and wrote the manuscript. X-zJ, Y-fY, and WH supervised and edited the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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Levothyroxine Therapy in Elderly Patients With Hypothyroidism

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Levothyroxine (L-T4) treatment of overt hypothyroidism can be more challenging in elderly compared to young patients. The elderly population is growing, and increasing incidence and prevalence of hypothyroidism with age are observed globally. Elderly people have more comorbidities compared to young patients, complicating correct diagnosis and management of hypothyroidism. Most importantly, cardiovascular complications compromise the usual start dosage and upward titration of L-T4 due to higher risk of decompensating cardiac ischemia and -function. It therefore takes more effort and care from the clinician, and the maintenance dose may have to be lower in order to avoid a cardiac incidence. On the other hand, L-T4 has a beneficial effect on cardiac function by increasing performance. The clinical challenge should not prevent treating with L-T4 should the patient develop e.g., cardiac ischemia. The endocrinologist is obliged to collaborate with the cardiologist on prophylactic cardiac measures by invasive cardiac surgery or medical therapy against cardiac ischemic angina. This usually allows subsequent successful treatment. Management of mild (subclinical) hypothyroidism is even more complex. Prevalent comorbidities in the elderly complicate correct diagnosis, since many concomitant morbidities can result in non-thyroidal illness, resembling mild hypothyroidism both clinically and biochemically. The diagnosis is further complicated as methods for measuring thyroid function (thyrotropin and thyroxine) vary immensely according to methodology and background population. It is thus imperative to ensure a correct diagnosis by etiology (e.g., autoimmunity) before deciding to treat. Even then, there is controversy regarding whether or not treatment of such mild forms of hypothyroidism in elderly will improve mortality, morbidity, and quality of life. This should be studied in large cohorts of patients in long-term placebo-controlled trials with clinically relevant outcomes. Other cases of hypothyroidism, e.g., medications, iodine overload or hypothalamus-pituitary-hypothyroidism, each pose specific challenges to management of hypothyroidism; these cases are also more frequent in the elderly. Finally, adherence to treatment is generally challenging. This is also the case in elderly patients, which may necessitate measuring thyroid hormones at individually tailored intervals, which is important to avoid over-treatment with increased risk of cardiac morbidity and mortality, osteoporosis, cognitive dysfunction, and muscle deficiency.

Keywords: levothyroxine, thyroid treatment, elderly, hypothyroidism, older adults, thyroid

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INTRODUCTION

According to World Population Prospects 2019 (United Nations, 2019), the proportion of the population aged 65 years or over has risen from 6% in 1990 to 9% in 2019 and it is expected to rise further to 16% by 2050 (1). The average life expectancy has undergone the fastest rise between 2000 and 2016 since the 1960s (2) and survival beyond age 65 is globally improving, as a person aged 65 years in 2015–2020 could expect to live, on average, an additional 17 years. Unsurprisingly, this demographic progress is accompanied by increasing prevalence of multiple chronic diseases, increased (multi)morbidity and disability and consequently polypharmacy with higher risk of drug interactions and adverse effects (3).

Hypothyroidism is a common condition caused by thyroid hormone deficiency. Most commonly, the pathology is within the thyroid gland and hence termed primary hypothyroidism, which biochemically is characterized by increased serum thyroid-stimulating hormone (TSH) concentrations. It is subdivided depending on the circulating free thyroxine (fT4) concentrations into overt hypothyroidism when fT4 was lower than the population-based reference range and subclinical hypothyroidism, when fT4 was within the population-based reference range (4). The latter is in turn subdivided into grade 1 (mild) subclinical hypothyroidism, when TSH is between the upper normal limit and 10 mU/l, and grade 2 (severe) subclinical hypothyroidism when TSH is ≥10 mU/l (5).

The prevalence of overt hypothyroidism in the general population ranges from 0.1 to 2% (6–9), while the prevalence of subclinical hypothyroidism is much higher varying from 4 to 10% (6, 8, 10, 11). The prevalence of hypothyroidism increases with age and subclinical hypothyroidism affects up to 15% of adults 65 years of age or older, when non-age-specific TSH reference ranges are used (9, 12–14). Spontaneous hypothyroidism is about 10 times more prevalent in women compared to men (15). By each age decade the proportion of women with increased serum TSH concentrations was higher compared with the one of men in the Colorado Thyroid Disease Prevalence study (9).

CHALLENGES IN THE DIAGNOSIS OF HYPOTHYROIDISM IN THE ELDERLY

Hypothyroid symptoms are non-specific and vary among patients, especially in the setting of subclinical hypothyroidism. The same symptoms are also quite common in euthyroid individuals and thus often overlap with the symptoms developed in patients with hypothyroidism (9). Although hypothyroidism-associated symptoms may indicate and identify hypothyroidism in most young patients, this is rarely the case in the elderly (16). Conversely, actual hypothyroidism causing tiredness, sleep disorders, depression, lack of concentration and amnesia in old individuals may be overlooked as these symptoms can be interpreted as normal age-related changes by both physicians and patients.

Convincing evidence during the last decades has shown an age-dependent shift in TSH distribution towards higher concentrations with increasing age. In the NHANES III study, median TSH concentrations progressively increased with age and the 97.5th percentiles were considerably higher in the >70 years old reference population without thyroid antibodies (97.5th percentile TSH in the reference population: total 4.1 mU/l; 70–79 yo 5.9 mIU/l; >80 yo 7.5 mU/l) (11). Similar results were obtained in other populations, such as in Scotland (97.5th percentile TSH 4.0, 5.5 and 5.9mU/l for 31–40 yo, 80–90 yo and >90 yo, respectively), in Ashkenazi Jews (4.6 and 7.2 mU/l at a median age of 72 and 98 years, respectively), in Americans (5.2 and 6.8 mU/l for 20–29 yo and >80 yo, respectively) and in Chinese (6.6 and 8.9 mU/l in <65 yo and ≥65 yo, respectively) (17–20). Iodine intake and thyroid autoimmunity are important factors to consider when looking at the epidemiology of hypothyroidism across ages and in any populations (21–23). Even a cautious iodine fortification in a population can change the incidences rather dramatically (21, 24, 25). Autoimmune hypothyroidism is the most common cause of hypothyroidism at all ages and the prevalence of thyroid autoimmunity increases with aging (23, 26, 27).

Nevertheless, the higher prevalence of thyroid autoimmunity in the older population can only partially explain the higher TSH concentrations with increasing age. Thus, among the thyroid antibody negative persons from the NHANES III study there was an age-dependent increase in TSH concentrations and longitudinal data have suggested that TSH generally increases over time and with age in the same subject especially in older individuals (28, 29). The interindividual age-dependent TSH rise was not associated with a decline in fT4 nor with increased mortality, suggesting that the TSH increment might reflect an age-related alteration in the TSH set point and/or reduced TSH bioactivity and/or reduced sensitivity of the thyroid gland to TSH rather than occult thyroid disease (30). When age-specific reference ranges were employed in the NHANES III study, 70% of the >80 yo group was reclassified as having normal for their age TSH rather than high TSH based on the reference range of the general population (>4.5 mU/l) (31). In addition, when the age-adjusted TSH reference ranges were used, no association between thyroid function and quality of life, mood, and cognition at baseline nor over the 5–8 years of follow-up in community-dwelling older men was found (32).

Longevity was associated with higher TSH concentrations in the Ashkenazi population (19) and confirmed by two Dutch studies (the Leiden 85-Plus Study and the Leiden Longevity Study) (33–35). Men and women aged 85 years with abnormally high TSH concentrations according to the general reference range for younger people and abnormally low concentrations of fT4 had the lowest mortality rate during the 3.7-yr follow-up (33). Analysis of combined data from nonagenarians from long-lived families from the Leiden Longevity Study and nonagenarians from the general population from the Leiden 85-Plus Study revealed an association between risk of mortality and lower fT4, higher free thyronine (fT3) and higher fT3/fT4 ratio, but not with higher TSH (36). The lower basal metabolic rate due to lower fT4 activity has been proposed as a possible explanation for the association between TSH and longevity (35).

A drug review process should always be conducted before the diagnosis of hypothyroidism. This is especially important for the older people as they very often present with increased (multi) morbidity and excess amount of prescribed medications. A number of medications can affect the thyroid function tests not only by interfering with the synthesis, transport, and metabolism of TSH and thyroid hormones but also by interfering with thyroid function immunoassays (30, 37–40) (**Table 1**).

The much more prevalent comorbidities in the elderly may result in alterations in thyroid function as part of the euthyroid sick syndrome. Although the euthyroid sick syndrome classically presents in critically ill patients (41, 42), it can also develop in the setting of common chronic conditions such as heart, kidney, liver disease, diabetes, major depression, as well as low caloric intake (43). The biochemical hallmark of the euthyroid sick syndrome is very low T3 concentrations in the presence of normal or slightly decreased TSH (**Figure 1**) (**Table 2**) (41, 42), and thus a T3 measurement should be performed if euthyroid sick syndrome is suspected. On progression a low T4 is usually observed as well, while TSH is often elevated in the restoration phase (41, 42). To date, treatment with L-T4 is not indicated in this situation, with the exception of patients in whom pre-existing primary hypothyroidism and euthyroid sick syndrome co-exist.

INDICATION FOR LEVOTHYROXINE TREATMENT OF HYPOTHYROIDISM IN ELDERLY

The indication for L-T4 treatment of overt hypothyroidism is similar in young and elderly hypothyroid patients. However, more caution must be paid to a variety of the complicating factors that are more prevalent with increasing age. Firstly, a correct diagnosis is more complicated due to the many possible comorbidities that can give rise to a falsely elevated serum TSH concentration even above 10 mU/L as required for the diagnosis of overt hypothyroidism due to (a) recovery from a lowered serum TSH seen in severe nonthyroidal illnesses (**Figure 1**), (b) recovery after different types of destructive thyroiditis (subacute, autoimmune, symptomless autoimmune thyroiditis), (c) medications such as lithium (treatment for bipolar maniodepressive psychosis), the antiarrythmic drug amiodarone, and glucocorticoids, which can inhibit thyroid hormone synthesis and metabolism and may cause transient reversible elevation of serum TSH (d) immune modulating drugs for treatment of other autoimmune diseases and cancers with ability to induce a transient autoimmune type of thyroiditis as in (b) (39), and (e) presence of big TSH or heterophile antibodies in the patient's serum (**Table 1**, **Table 2**).

A complimentary measurement of fT4 estimate must be done in all cases (either by total T4 combined with a measure of binding proteins or by one of the fT4 clinical biochemical platforms used in laboratories worldwide), while measurement of serum T3 is not recommended for the treatment indication of hypothyroidism (15); T3 may be relevant for identifying euthyroid sick syndrome, though. T4 measurements can give rise to falsely low concentrations in case of molecular changes in the thyroid hormone binding proteins in serum: thyroxine binding globulin, transthyretin, or albumin or through their binding affinity for T4. Circulating T3- or T4- binding autoantibodies can cause methodological artefacts in both total and free measurements of T4 (40, 45–47) as can antibodies against assay reagents (e.g., antiruthenium, antistreptavidin,

TABLE 1 | Drugs with an increased likelihood of inducing thyroid dysfunction.

Inhibit thyroidhormone production	Alter extra-thyroidal metabolismof thyroid hormone	Alter T4/T3 bindingto plasma proteins	Induction of thyroiditis	Affection of TSH secretion	Impairing absorption of oral T4
Antithyroid drugs Amiodarone	Propylthiouracil Glucocorticoids	Estrogen Heroin	Amiodarone Interleukin-2	Lithium Dopamine Receptor Blockers	Aluminum hydroxide Ferrous Sulfate
Lithium Iodide (large doses) Iodine-containing contrast media	Propranolol Amiodarone Iodine-containing contrast media	Methadone Clofibrate 5-Fluorouracil	Interferon-α Interferon-β γ-Interferon	L-Dopa Inhibitors Cimetidine Clomifene	Cholestyramine Calcium Carbonate Calcium Citrate
	Carbamazepine Barbiturates	Perphenazine Glucocorticoids	Sunitinib Monoclonal antibody therapy (the check point inhibitors: Nivulomab, Pembrolizumab, Ipilimimab)	Thyroid Hormone Dopamine	Calcium Acetate Iron Sulfate
	Rifampicin Phenytoin Sertralin	Androgens L-Asparaginase Nicotinic Acid Furosemid Salicylates Phenytoin Fenclofenac Heparin		L-Dopa Glucocorticoids Growth Hormone Somatostatin Octreotide	Colestipol Sucralfate Soya preparations Kayexalate Ciprofloxacin Sevelamer Proton pump inhibitors
Other Thalidomide Lenalidomide Chemotherapy for sarcoma					

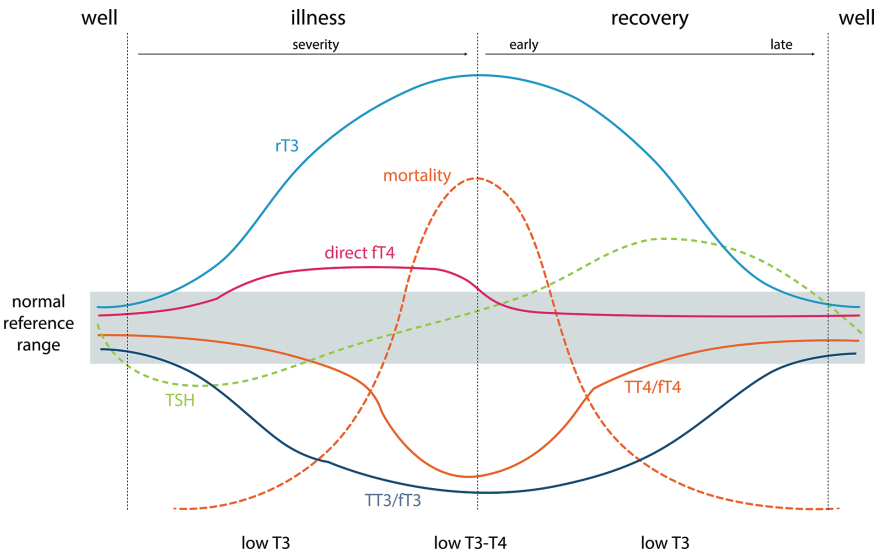

FIGURE 1 | Typical changes in thyroid function tests during the development of and recovery from nonthyroidal illness and their relationship to mortality. TSH, thyrotropin; TT3/TT4, total thyroid hormones; FT3/FT4, measured free thyroid hormone estimates; direct FT4, direct measurement of free T4 by dialysis or ultrafiltration = "True free T4"; rT3: reverse T3. Adapted from Demers and Spencer eds. (44).

TABLE 2 | Some situations in which serum TSH alone can give a false or uncertain indication of thyroid status in elderly people compared to the normal reference interval in young persons.

Condition	TSH	fT4	fT3
Primary abnormality/change of TSH secretion			
Increasing age	H	N	N
Pituitary-hypothalamic abnormality	L-N	L	L
Central TSH excess	N-H	H	H
Hyperthyroidism			
T3 toxicosis	S	N	H
Subclinical	S	N	N
Early Treatment with antithyroid drugs	S	H-N-L	H-N-L
TSH assay artefact	L-N-H	H	H
Hypothyroidism			
Subclinical	H	N	N
Early Treatment with levothyroxine	H	L-N	L-N
TSH assay artefact	H	N	N
Thyroid hormone resistance	N -H	H	H
Euthyroid Sick syndrome and recovery	L-N-H	L-N	L
Medications			
Dopamine	L	N	N
Glucocorticoids	L	N	L-N
Amiodarone (acute)	H	N-H	L

N, normal; L, low; H, high; S, suppressed.

or antibiotin). High dose biotin ingestion by the patient has also been shown to result in serious distortion of analyte- and platformspecific assay results, and is now a frequent cause of false results due to the current popularity of biotin ingestion for skin and hair beauty products (47). To increase the likelihood of true hypothyroidism and not only a biochemical quirk it is helpful to search for the etiology of the disease, such as presence of anti-peroxidase antibodies in thyroid autoimmunity, history of previous surgery or radioiodine therapy or other important causes.

When the diagnosis is secured eventually by reanalysis of samples drawn after 3–6 months and/or testing in a different laboratory using different measurement methodology, the clinician will be faced with the challenge of assessing the current cardiac situation of the patient. Hypothyroidism has a profoundly negative effect on cardiac performance (**Table 3**) which results in low exercise performance, and more prominently so in elderly patients. This is particularly the case in patients with a pre-existing heart failure, which should always be considered a possibility in the evaluation of older patients with hypothyroidism (48, 49). Even in asymptomatic individuals it is therefore pertinent to perform a very rigorous assessment of elderly hypothyroid patients before commencement of L-T4 therapy in order to avoid provoking cardiac ischemia and/or insufficiency by increasing the resting metabolic rate. In case of very high age and/or suspicion of a cardiac condition the patient

TABLE 3 | Hemodynamic changes in hypothyroidism.

Myocardial contractility	↓
Peripheral vascular resistance	↑
Circulation time	↑
Diastolic blood pressure	↑
Arterial stiffness	↑
Left ventricular stroke volume	↓
Left ventricular systolic function	↓
Left ventricular diastolic function	↓
Cardiac output	↓
Cardiac index	↓
Exercise tolerance	↓

may require a stress test or coronary angiography to aid in the risk assessment. In case of any cardiac issues it is wise to consult a cardiologist also to discuss possible relevant prophylactic treatment options, to open the vessels surgically in case of stenosis or by antianginous medications (50). It is also sometimes prudent to start levothyroxine therapy in patients with cardiac conditions during hospitalization and monitoring of cardiac rhythm and function.

It is important to realize that normal thyroid function and thus also L-T4 therapy of overt hypothyroidism is eventually beneficial for cardiac function (**Table 4**) (51), so it is clinically imperative to make an effort to persuade the patient to comply with the treatment even if there are obstacles to starting the therapy.

Both diagnosing and decision of treatment or not are much more difficult in patients with mild or subclinical hypothyroidism in the elderly for a variety of reasons (5). The diagnosis is more challenging than that of overt hypothyroidism due partly to all of the above mentioned complicating and confounding factors being even less clear in discriminating between normal thyroid function and mild hypothyroidism in elderly persons compared with young ones: (a) The upper reference limit of serum TSH concentrations in healthy normal elderly people is highly variable with age and not studied in populations at large, nor by different laboratory platforms. Ideally, each laboratory should perform its own age specific population specific reference interval across the age range including centenarians in order to diagnose the condition correctly. This, however, rarely happens. The upper limit of serum TSH in the older population can be up to 7.5–8.8 mU/L which does not leave much space up to 10 mU/L when also considering the method related imprecision of serum TSH measurements (**Table 2**). (b) Symptoms are milder and less discriminative in the elderly. (c) It puts a strong responsibility on clinicians to make sure to diagnose correctly and avoid misclassification resulting in incorrect commencement of L-T4 (**Table 2**). This is so much more important because the risk of overdosing is high in the elderly and treatment with L-T4 of persons with normal thyroid function but with variable symptoms that might be due to hypothyroidism is strongly advised against (4, 15). (d) The presence of thyroid antibodies, which is associated with an increased risk of progression from subclinical to overt hypothyroidism, suggests a closer monitoring of thyroid function in subjects with thyroid antibodies (27, 52). On the contrary, normalization of TSH occurs more often in thyroid antibodies negative subjects. (e) L-T4 therapy is more challenging in elderly patients with many comorbidities and multipharmacy with drugs that can also influence the absorption of T4 (53) (**Tables 1** and **2**); not to forget difficult compliance in patients receiving a multitude of drugs.

The frailty status is another important factor to consider before initiation of LT4 treatment of elderly people with subclinical hypothyroidism. The frail elderly are vulnerable to drugs side effects, overtreatment and poor compliance (54). These considerations as well as a possible positive effect of thyroid autoimmunity on frailty status (55) suggest a conservative wait-and-see approach for frail older patients even in the presence of thyroid autoimmunity (54).

Some of these challenges can be overcome by getting a good overview of the patient's concomitant diseases, or eventually look for other likely candidates as explanation for the patient's complaints such as presence of other autoimmune diseases, particularly those that might compromise T4 absorption such as pernicious anemia, coeliac disease and ulcerative colitis (56), or by prescribing other T4 formulations such as an easily absorbable gel capsule (57, 58).

TABLE 4 | Treatment of hypothyroidism with levothyroxine—cardiac concerns and effects on these risk factors.

Concerns	Effects
Cardiac insufficiency	Normalizes cardiac output
Ischemia and angina pectoris	Normalizes left ventricular contractile performance
Tachyarrhythmias	Lowers diastolic blood pressure
Pericardial effusion	Decreases serum cholesterol
High output failure without preexisting heart disease	Normalizes diastolic dysfunction
	Normalizes endothelial dysfunction

TITRATION OF LEVOTHYROXINE THERAPY IN ELDERLY PATIENTS AND MONITORING OF EFFECT

Due to the vague symptoms of subclinical hypothyroidism also in the elderly, the diagnosis is often suggested by incidental discovery of a high TSH within a package of blood measurements in persons showing up at the general practitioner for being tired. Anyway, if deciding on performing a therapeutic trial together with the patient, proper treatment monitoring and particularly avoiding overdosing is extremely important not to put the patient at risk.

Once a patient-clinician agreement on initiating levothyroxine treatment has been reached, three main issues are particularly relevant in the elderly patient, in order to ensure appropriate treatment: Is cardiac comorbidity present? How should treatment be initiated? What is the treatment target to aim for?

In case cardiac co-morbidity has been ruled out, possibly in collaboration with a cardiology expert, it seems safe to start similarly as in younger patients (59); nonetheless, most clinicians start at lower doses and up-titrate at a slower pace, acknowledging the general frailty of this age-group.

Lacking good evidence the treatment target is mostly empirically based and could be either (a) TSH (ideally related to an age specific reference range), (b) other biochemical and clinical indices of thyroid function or (c) patient-experienced variables, e.g., thyroid-related patient-reported outcomes (PRO). Usually, serum TSH concentrations are aimed at a higher TSH than in younger patients, respecting the possibly better health outcomes associated with higher TSH in old age (4, 53). Similarly, fT4 is aimed at a concentration in the lower half of the reference range.

However, no trials have substantiated this approach, since no blinded randomized placebo-controlled trials of L-T4 treatment in elderly patients with hypothyroidism comparing different TSH targets have been published.

Blood-lipids are frequently monitored during L-T4 therapy as indication of treatment effect. However, there is no reliable laboratory index of peripheral thyroid hormone action, but some tests (27, 60), including sex steroid- binding globulin, serum ferritin, serum angiotensin- converting enzyme, as well as oxygen consumption (resting energy expenditure), systolic time interval, and cardiac contractility (61, 62), may be useful in rare unclear cases of following the individual response in situations of suspected thyroid hormone resistance or during long-term suppressive therapy with T4.

Due to its long history, introduction of L-T4 treatment for overt hypothyroidism was not preceded by modern randomized clinical trials (63) and thus data on patient-reported outcome of treatment mostly rely on observational studies. Generally, levothyroxine treatment has been shown to improve QoL (including symptoms) in patients with hypothyroidism (62). However, since symptoms and thus the patient-experienced manifestations of hypothyroidism are vaguer among the elderly (16), effects observed in younger populations cannot unquestionably be extrapolated to older ones. The limited symptomatology implies smaller patient-experienced treatment effects, which may also decrease motivation for treatment initiation and adherence in individual patients.

The fewer symptoms in older patients will also impede recognition of a potential treatment effect in randomized clinical trials. This may particularly be the case in patients with subclinical hypothyroidism and may have influenced the negative findings in previous randomized clinical trials (64), reviewed by Feller et al. (65). However, secondary analyses in patients with higher symptom loads from the largest trial among elderly patients corroborated the lack of patient-experienced effect (66). Regrettably, no counterpart to the above mentioned randomized clinical trial by Stott et al., has been conducted in patients with overt disease; even well-designed descriptive longitudinal studies exploring the effect of L-T4 treatment on quality of life among elderly are lacking (14).

Apart from titrating L-T4 to an appropriate biochemical target, a classical patient-physician encounter in terms of the physician inquiring about symptoms of over-replacement as part of a clinical interview is paramount for proper management. To date, no studies evaluating a systematic approach to symptom monitoring *via* patient-reported outcomes have been published, although it may offer a valuable source of information and facilitate adherence.

Challenges are also faced when treating secondary hypothyroidism, including central hypothyroidism, in the elderly. Since TSH cannot be applied as a titration target, fT4 in the upper level of the reference range is normally recommended as target (53, 67). However, no clinical evidence is available on how the cautious strategy regarding L-T4 replacement in elderly patients with primary hypothyroidism (a higher TSH) should be translated into their counterparts with secondary hypothyroidism. It seems prudent to aim for fT4 in the lower half of the reference range in older patients, paying attention to lipids and body mass index (68–70), and closely monitoring symptoms and signs of overtreatment. Randomized clinical trials targeting various fT4 ranges and evaluating other clinical measures of thyroid function and QoL are also in this situation highly warranted.

ADHERENCE AND RISK OF OVERTREATMENT IN ELDERLY PATIENTS WITH HYPOTHYROIDISM

The limited QoL-impact of hypothyroidism and the associated subtle treatment effect experienced in elderly patients challenges treatment motivation and thus adherence. As mentioned above, polypharmacy, a high degree of co-morbidity, particularly cognitive co-morbidity, further challenge adherence. For the latter, the often-complex L-T4 regimen, with doses varying over weekdays to achieve optimal titration, may be a particular challenge. Polypharmacy also leads to difficulties obtaining ideal absorption; patients with e.g., dementia may have difficulty taking levothyroxine separate from other medications and in the fasting state, as generally recommended. Management strategies to counteract these obstacles may involve dosing boxes and possibly even weekly dosing. Efficacy of such action remains to be elucidated, as does e.g. a potentially useful dosing at bedtime, separate from other medication (71). In case L-T4 tablet malabsorption is suspected, different formulation of L-T4 (e.g., liquid or gel) could be considered (57, 58).

In other diseases, particularly within oncology and rheumatology, implementation of PROs as monitoring and communication tools has led to improved patient-clinician interaction and patient satisfaction (72). A groundbreaking study by Basch et al. showed improved management, QoL, morbidity, health care use and mortality, when implementing a systematic patient-reported symptom monitoring system among cancer patients (73). Unexpectedly, the effect was strongest in patients with the least resources and education. It is possible, that implementation of such a system, within the electronic health records of elderly patients with overt or subclinical hypothyroidism, would guide treatment decisions, including a decision to abstain from treatment of subclinical hypothyroidism in case of no recognizable patient-reported effect, improve treatment adherence and identify adverse effects. In practice, patients would complete a standardized, validated PRO prior to their appointment with their endocrinologist/physician, the results of which would be entered directly into the health record. In case the PRO results are presented in a comprehensible way, as e.g., illustrated in **Figures 2A, B**, it may form a useful communication tool between the patients and their health caretakers (74). As a tool for monitoring of and improving adherence to L-T4 treatment, the ThyPRO appears to be a relevant candidate (75, 76), given its wide application and well-documented validity (77). The multidimensional results of a ThyPRO completion is often displayed as a radar-plot, as in **Figure 2C**, but an optimal format for patient communication still remains to be established.

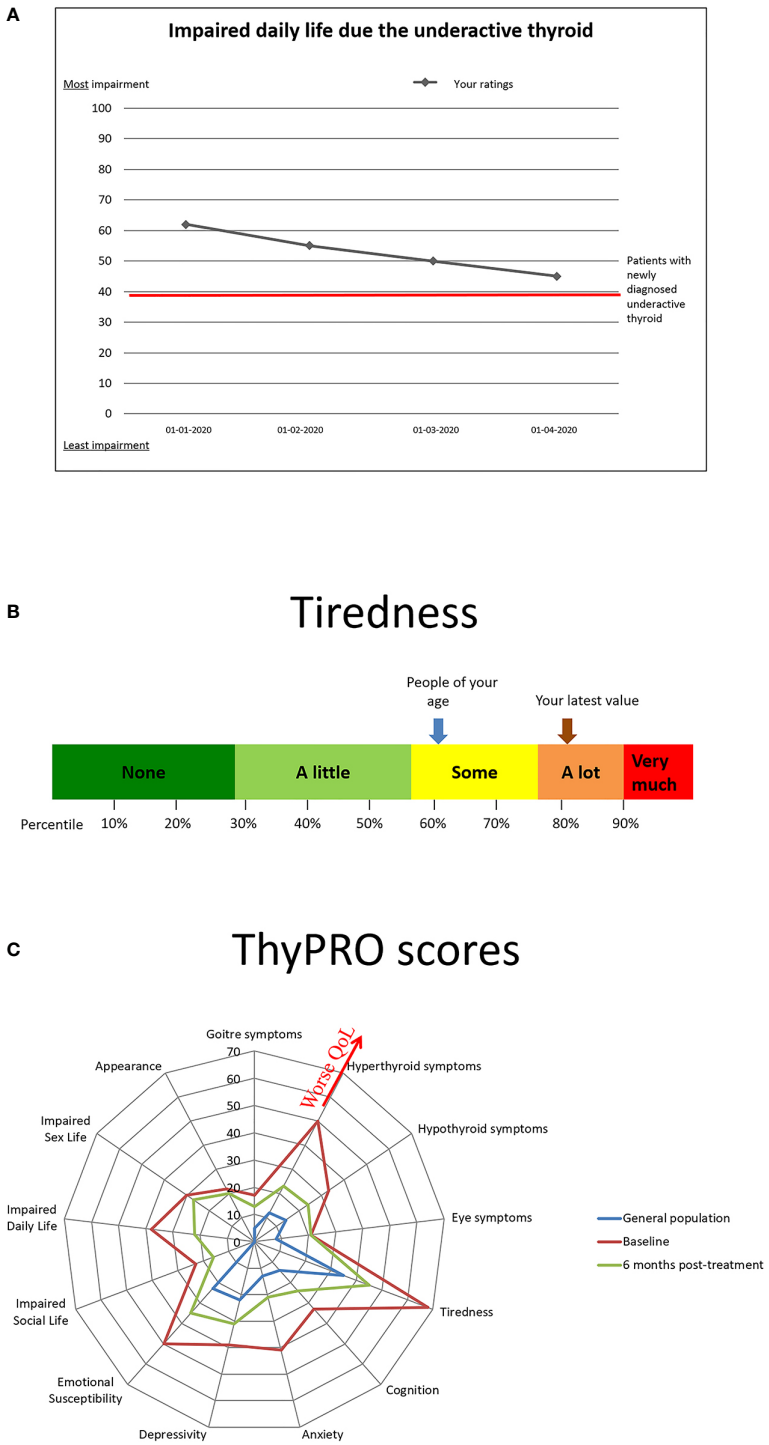

FIGURE 2 | Examples of presentations of results from patient-reported outcomes recorded prior to a patient visit. **(A)** Patient-oriented presentation with reference to previous ratings. **(B)** Patient-oriented presentation with reference values as percentiles and general population reference. **(C)** Clinician-oriented multidimensional quality of life (QoL) presentation.

Studies evaluating the effect of implementing PRO measures in clinical management of hypothyroidism among the elderly (or in any thyroid population) are still awaited.

The risk of overtreatment with L-T4 cannot be overemphasized especially in the elderly (9, 78–80). Five to 24 percent of all patients taking L-T4 develop iatrogenic thyrotoxicosis (9, 11, 78, 81–83),

a proportion that is even higher in the elderly [up to 41% (79)]. Approximately half of the prevalent and incident low TSH events are related to overtreatment with L-T4, with the highest rates among older women (84). Overtreatment is associated not only with a suppressed TSH concentration but may also result in higher concentrations of fT4 compared with healthy controls (27). Thyroid hormones in excess are catabolic on the one hand while essential for stimulating the general basic metabolic rate (resting energy expenditure) on the other (85, 86). Overtreatment with L-T4 thus results in adverse effects due to acceleration of these physiological effects (85, 86). Consequently, overstimulating the catabolic metabolism is putting too high a pressure on the human organism which will eventually lead to loss of important and vital functions from failing productions of vital organ components.

Thus, suppressed TSH has in population studies consistently been associated with a higher mortality and other adverse effects compared to people with normal or even higher TSH concentrations (**Table 5**) (87–90). Apart from the higher mortality in patients with suppressed TSH the most important risks of overtreatment are those affecting the heart (50), the bones (91), the brain (92) and muscle function (93). Many of the studies on the effect of a higher thyroid function than normal on the various organ risks, however, come from patients with endogenously elevated thyroid hormones and suppressed TSH, which can nevertheless be considered a surrogate for iatrogenic hyperthyroidism as described below.

Older patients with low TSH and higher fT4 have a higher prevalence and incidence of atrial fibrillation compared with euthyroid subjects (94–98), >5-fold higher likelihood for the presence of atrial fibrillation in both patients with subclinical and overt hyperthyroidism (98). In addition, the serum fT_4 concentration was independently associated with atrial fibrillation in euthyroid subjects 65 years and older (95) and old individuals with TSH in the lowest quartile and fT4 in the highest quartile of the normal range had an increased risk of atrial fibrillation (99). Finally, thyroid-cancer patients receiving TSH suppressive doses of L-T4 had increased risk of cardiovascular and all-cause mortality (100).

Most data on the skeletal effects of thyroid hormone excess support increased bone loss and risk of fractures in post-menopausal women and elderly men with thyrotoxicosis. Subclinical hyperthyroidism was also associated with greater annual bone loss at the femoral neck but not at the lumbar spine in prospective cohorts (101), while in euthyroid women with a history of Graves' hyperthyroidism lumbar spine bone density was negatively associated with TSH receptor antibodies in post- but not premenopausal women (102). L-T4 treated women with low TSH concentrations lose bone mineral from the spine more rapidly compared with women without known thyroid disease (103), and TSH-suppressive therapy was associated with a significant bone loss at both the lumbar spine and hip in postmenopausal, but not in premenopausal, women (91). Increased bone loss and risk of fracture was also found in euthyroid postmenopausal women with fT4 and/or fT3 levels within the upper normal range and in older adults with low TSH (104–106). The effect of current use of L-T4 treatment in elderly on the risk of fractures seems dose-related (107), particularly in women aged ≥65 years with osteoporosis (108). Additionally, the risk of a non-vertebral fracture was increased in euthyroid postmenopausal women with higher fT4 and/or fT3 (104). Recently, radiological vertebral fractures in women with differentiated thyroid carcinoma receiving post-surgical levothyroxine treatment were significantly and independently associated with TSH <1.0 mU/l, age of patients, duration of L-T4 therapy and densitometric diagnosis of osteoporosis at any skeletal site (109).

It is not very clear if overtreatment with L-T4 causes cognitive and psychiatric disturbances as well as an impairment of QoL, but endogenous thyrotoxicosis is well known to have the capability to result in these brain affections (110–112), and can likely be used as surrogate markers for L-T4 overtreatment. Prospective studies, however, are needed for further clarification of the long-term risk of brain dysfunction in cases of overtreatment with T4.

Thyrotoxicosis induces a reduction of muscle mass (113) and few studies in young or non-elderly subjects have demonstrated reduced muscle strength, which is restored after normalization of thyroid hormones (114–119). In newly diagnosed patients with Graves' disease the hyperthyroidism was associated with impaired maximum muscle strength, performance, and balance (120). However, in older adults, subclinical hyperthyroidism was not associated with low muscle mass and/or strength (121–123), but the association between TSH and low muscle strength was found to be U-shaped (123). Nevertheless, data on the association between T3/fT3 and muscle mass are conflicting and some studies found negative (35, 123), while others positive associations (124–126), with some differences between men and women.

TABLE 5 | Major risks from overtreatment with levothyroxine of elderly patients with overt or subclinical hypothyroidism.

Cardiac arrythmias (atrial fibrillation or other tachyarrythmias)
Global decrease in cardiac physical performance
Progressive heart failure
Loss of bone mineral content progressing to osteoporosis
Progressive catabolic muscle loss progressing to muscle insufficiency
Other catabolic consequences such as loss of protein and vitamins and other substances
Cognitive disturbance progressing to premature dementia
Progressive impairment of quality of life
Premature death - most often cardiac

FUTURE CLINICAL TRIALS AND DEVELOPMENTS

Evidently, further documentation on several aspects of L-T4 treatment in elderly patients are warranted.

First of all, large randomized clinical trials among elderly patients with overt hypothyroidism targeting different TSH titration ranges are needed to guide future clinical practice.

Secondly, large randomized clinical trials evaluating safety and efficacy of L-T4 for subclinical hypothyroidism, ideally in

several strata of TSH both at inclusion and as target, are needed for a personal medication approach to be evidence-based.

Thirdly, in both above trial settings, safety, including all aspects of risk of overreplacement should be investigated.

Fourthly, trials evaluating usefulness of implementing PRO measurements in L-T4 treatment and monitoring of elderly patients with both overt and mild/subclinical hypothyroidism should be performed, in order to evaluate, if such an approach provides value for clinicians and patients.

Finally, new biomarkers of thyroid function metabolism for monitoring efficacy of L-T4 therapy in the elderly should be sought for and, along with already existing candidates, evaluated properly in clinical studies.

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Levothyroxine Treatment and Cardiovascular Outcomes in Older People With Subclinical Hypothyroidism: Pooled Individual Results of Two Randomised Controlled Trials

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Background: The cardiovascular effects of treating older adults with subclinical hypothyroidism (SCH) are uncertain. Although concerns have been raised regarding a potential increase in cardiovascular side effects from thyroid hormone replacement, undertreatment may also increase the risk of cardiovascular events, especially for patients with cardiovascular disease (CVD).

Objective: To determine the effects of levothyroxine treatment on cardiovascular outcomes in older adults with SCH.

Methods: Combined data of two parallel randomised double-blind placebo-controlled trials TRUST (Thyroid hormone Replacement for Untreated older adults with Subclinical hypothyroidism – a randomised placebo controlled Trial) and IEMO80+ (the Institute for Evidence-Based Medicine in Old Age 80-plus thyroid trial) were analysed as one-stage

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individual participant data. Participants aged ≥65 years for TRUST (n=737) and ≥80 years for IEMO80+ (n=105) with SCH, defined by elevated TSH with fT4 within the reference range, were included. Participants were randomly assigned to receive placebo or levothyroxine, with titration of the dose until TSH level was within the reference range. Cardiovascular events and cardiovascular side effects of overtreatment (new-onset atrial fibrillation and heart failure) were investigated, including stratified analyses according to CVD history and age.

Results: The median [IQR] age was 75.0 [69.7–81.1] years, and 448 participants (53.2%) were women. The mean TSH was 6.38± SD 5.7 mIU/L at baseline and decreased at 1 year to 5.66 ± 3.3 mIU/L in the placebo group, compared with 3.66 ± 2.1 mIU/L in the levothyroxine group (p<0.001), at a median dose of 50 μg. Levothyroxine did not significantly change the risk of any of the prespecified cardiovascular outcomes, including cardiovascular events (HR 0.74 [0.41–1.25]), atrial fibrillation (HR 0.69 [0.32–1.52]), or heart failure (0.41 [0.13–1.35]), or all-cause mortality (HR 1.28 [0.54–3.03]), irrespective of history of CVD and age.

Conclusion: Treatment with levothyroxine did not significantly change the risk of cardiovascular outcomes in older adults with subclinical hypothyroidism, irrespective of a history of cardiovascular disease and age.

Clinical Trial Registration: [ClinicalTrials.gov], identifier [NCT01660126] (TRUST); Netherlands Trial Register: NTR3851 (IEMO80+).

Keywords: cardiovascular disease, levothyroxine, randomised controlled trial, subclinical hypothyroidism, older adults

INTRODUCTION

Subclinical hypothyroidism (SCH) is a common condition in older adults, with a prevalence between 8% and 18% (1). SCH is defined by elevated levels of thyroid stimulating hormone (TSH) with free thyroxine (fT4) within the reference range. Patients with SCH are mostly asymptomatic, although SCH is a possible contributor to various health problems including cardiovascular diseases (CVD) (2). The cardiovascular effect of treating older adults with SCH is uncertain.

The cardiovascular system is sensitive to changes in thyroid hormone concentrations due to thyroid hormone receptors in myocardial and vascular endothelial tissues (3). Associations have been found between SCH and an increase in the number of cardiovascular risk factors (4). In addition, meta-analyses of prospective studies showed that SCH was associated with an increased risk of heart failure, major adverse cardiovascular events (MACE) and cardiovascular death (2, 5–7). Although associations have been found between SCH and CVD, data are limited and conflicting regarding the effect of treatment with levothyroxine on cardiovascular outcomes (3). Large randomised controlled trials (RCT) investigating especially cardiovascular outcomes in older patients are limited and most often investigated surrogate markers of CVD, such as cardiovascular risk factors (8) or cardiac function and structure (9–11). On the one hand, concerns have been raised regarding a potential increase in cardiovascular side effects from thyroid hormone replacement, such as atrial fibrillation and heart failure. On the other hand, undertreatment may increase the risk of cardiovascular events, especially for patients with CVD or older age.

Two recent RCTs, namely TRUST (Thyroid hormone Replacement for Untreated older adults with Subclinical hypothyroidism – a randomised placebo controlled Trial) and IEMO80+ (the Institute for Evidence-Based Medicine in Old Age 80-plus thyroid trial), reported the absence of beneficial effect of levothyroxine on thyroid specific quality of life related outcomes in older patients with SCH (12, 13). For the first time combining all data from the two trials, the aim of the present study is to assess the effect of levothyroxine treatment on cardiovascular outcomes in older adults with SCH.

MATERIALS AND METHODS

This study is a prespecified combined analysis of the TRUST and IEMO80+ studies. These studies were designed and executed as parallel trials with identical study protocols, both investigating whether levothyroxine provides clinical benefits in older persons with SCH.

An Institutional Review Board approved the studies prior to data collection. Written informed consent was obtained from all

Abbreviations: 95% CI, 95% confidence interval; EQ-5D, EuroQol Group 5-Dimension Self-Report Questionnaire; fT4, free thyroxine 4; HR, hazard ratio; IEMO80+, the Institute for Evidence-Based Medicine in Old Age 80-plus thyroid trial; IPD, individual participant data; RCT, randomised controlled trial; SCH, subclinical hypothyroidism; SD, standard deviation; SE, standard error; TRUST, Thyroid hormone Replacement for Untreated older adults with Subclinical hypothyroidism – a randomised placebo controlled Trial; TSH, thyroid stimulating hormone; ThyPRO, Thyroid Related Quality-of-Life Patient-Reported Outcome measure.

participants. Data were analysed as one-stage individual participant data (IPD) of these two randomised double-blind placebo-controlled trials. Detailed description and protocols have been published previously (14, 15). In summary, older participants (≥65 years for TRUST and ≥80 years for IEMO80+) with SCH, diagnosed by elevated TSH levels (4.6 to 19.9 mIU/L), measured on at least two occasions between 3 months and 3 years apart, with fT4 levels within the reference range, were enrolled in Ireland, Scotland, Switzerland and The Netherlands. Participants were randomised in a 1:1 ratio for levothyroxine or placebo, with titration of the levothyroxine dose according to TSH level every 6 to 8 weeks and a mock titration schedule with a similar frequency in the placebo group. The levothyroxine group started with a dose of 50μg daily (or 25μg for participants with weight <50kg or a history of coronary heart disease). Participants were followed up for a minimum of 12 months and a maximum of 36 months between April 2013 and May 2018. The final follow-up was on May 4, 2018.

Endpoints

The present analysis reports cardiovascular outcomes, including all-cause and cardiovascular mortality, and both cardiovascular events and cardiovascular side effects. Cardiovascular events are fatal and non-fatal cardiovascular events, including acute myocardial infarction, stroke, amputations for peripheral vascular disease, revascularisations for atherosclerotic vascular disease (including for acute coronary syndrome) and heart failure hospitalisations. Cardiovascular side effects of overtreatment include new-onset atrial fibrillation and new-onset heart failure. Secondary outcomes include the cardiovascular parameters blood pressure, heart rate and weight, which were measured as positive signals of TSH change.

History of Cardiovascular Disease and Age

Stratified analyses were executed for patients with or without a history of CVD at inclusion. CVD was defined as ischemic heart disease (both angina pectoris or myocardial infarction), stroke or transient ischemic attack, heart failure, peripheral vascular disease, revascularization or atrial fibrillation. Furthermore, patients were stratified in the 65 to 80 age range, or ≥80 years old.

Statistical Analysis

Baseline characteristics are presented as mean ± standard deviation (SD) or median [interquartile range (IQR)] depending on the distribution of data, stratified for history of CVD. Hazard ratios (HR) were obtained from a Cox proportional hazard regression model and were adjusted for country, sex, starting dose of levothyroxine and study, similar to previous publications (14, 15). Results at 12 months and between-group differences were adjusted for country, sex, starting dose of levothyroxine, study (TRUST or IEMO80+) as random effect and baseline levels of the same variable with the use of linear mixed models. Between-group differences are the value in the levothyroxine group minus the value in the placebo group. The efficacy and safety analyses were carried out in a modified intention-to-treat population, which included participants with data on the outcome of interest. The data were analysed using IBM SPSS Statistics, version 23. P-values were considered statistically significant if lower than 0.05. Interaction analyses were performed between treatment and history of CVD and all secondary endpoints.

RESULTS

In total, all 737 patients from TRUST and all 105 patients from IEMO80+ were included in this combined data-analysis, see **Figure 1**. Of the 842 participants who underwent randomization, 422 were assigned to receive placebo and 420 to receive levothyroxine. For the baseline characteristics see **Table 1**. The median age of the 842 participants was 75.0 [IQR 69.7–81.1] years, with 419 (56.9%) participants older than 80 years. In total, 448 participants (53.2%) were women and 302 (35.9%) had a history of CVD. History of CVD or cardiovascular risk factors did not differ between the placebo or levothyroxine group. Median follow-up was 17 months. A total of 368 participants (87.2%) of the placebo group and 363 (86.4%) of the levothyroxine group completed 12-month follow-up, which did not differ between patients with or without a history of CVD, see **Figure 1**. In total, 194 (23.0%) patients discontinued the trial regimen and 44 (5.2%) withdrew from follow-up. Most participants (83.8%) started with a dose of 50 μg and 16.2% with 25 μg levothyroxine. Of patients with a history of CVD, 58.9% started with a dose of 50 μg levothyroxine and of patients older than 80 79.5%.

Thyroid Function

The mean ± SD TSH was 6.38 ± 5.7 mIU/L at baseline, and decreased at 1 year to 5.66 ± 3.3 mIU/L in the placebo group, compared with 3.66 ± 2.1 mIU/L in the levothyroxine treated group ($p<0.001$), at a median dose of 50 μg. TSH did not differ significantly at baseline or at 12 months between patients with or without a history of CVD (p-interaction=0.31), see **Table 2**.

Cardiovascular Outcomes

In total, 44 (5.2%) fatal and non-fatal cardiovascular events occurred after a median follow-up of 17 months, which did not significantly differ between placebo and levothyroxine with a HR comparing treatment to placebo of 0.74 (0.41 to 1.35). Comparing cardiovascular side effects of overtreatment risk of new-onset atrial fibrillation was associated with levothyroxine treatment was HR 0.69 (0.32 to 1.52) and HR of new-onset heart failure was 0.41 (0.13 to 1.35). Furthermore, in total, 21 (2.5%) deaths from any cause occurred (of which 4 cardiovascular deaths) with a HR for levothyroxine treatment of 1.28 (0.54 to 3.03). **Figure 2** shows a forest plot of all cardiovascular outcomes, comparing placebo to levothyroxine stratified by history of CVD and age, showing that levothyroxine did not significantly change the risk of any of the cardiovascular outcomes, irrespective of CVD history or age (p for interaction all >0.10).

No clinically relevant or statistically significant adjusted differences between levothyroxine and placebo were found at 12 months for blood pressure, heart rate and weight (**Table 2**).

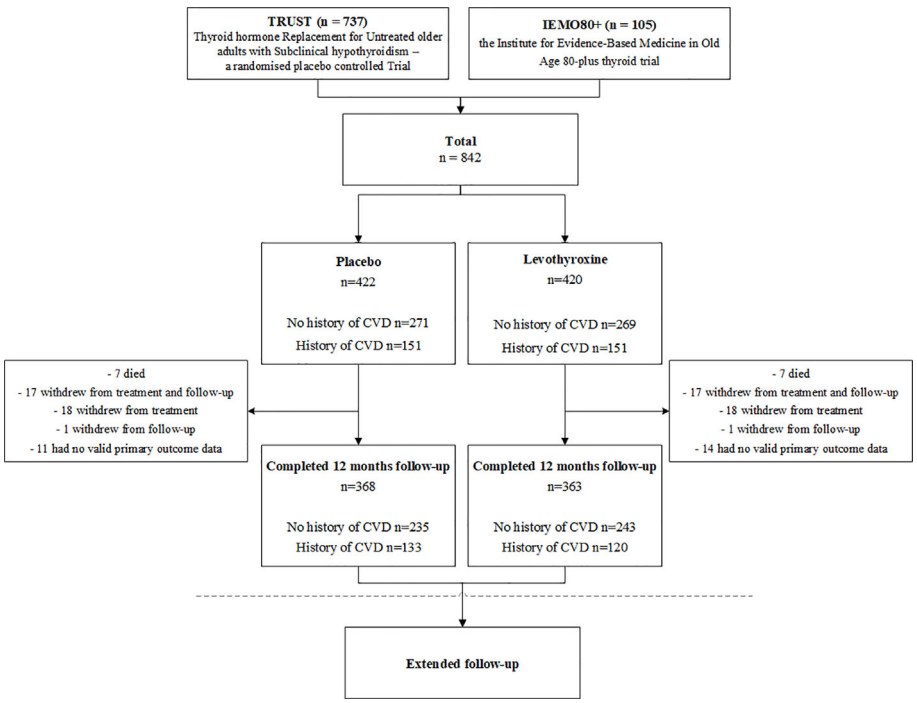

FIGURE 1 | Flowchart study population. Combined data of the TRUST and IEMO80+ trials will be examined as one-stage individual participant data of these two randomised double-blind placebo-controlled parallel group trials. Cardiovascular disease (CVD) is defined as ischemic heart disease, stroke or transient ischemic attack, heart failure, peripheral vascular disease, revascularisation or atrial fibrillation. Median follow-up was 17-months.

Outcomes did not differ between patients with or without a history of CVD (p for interaction all >0.10).

DISCUSSION

In this prespecified combined analysis of the TRUST and IEMO80+ trials, treatment with levothyroxine did not increase or decrease the risk of cardiovascular outcomes significantly in older adults with SCH, irrespective of CVD history and age.

In older patients with SCH, the current European and United States guidelines recommend no routine thyroid hormone therapy (16, 17). Especially in older people, treatment should be individualised, gradual and closely monitored. In the oldest old subjects, defined as >80 years old, SCH should be carefully followed with a wait-and-see strategy, generally avoiding hormonal treatment (16). The outcomes of both TRUST and IEMO80+ support this wait-and-see strategy as they showed no consistent beneficial effect of levothyroxine on quality of life, in both older (TRUST) and oldest old subjects (IEMO80+) (12, 13). Although experts have pointed out the need, before the TRUST and IEMO80+ studies, randomised trials investigating hard cardiovascular endpoints were lacking (18). Hence we sought to answer the question whether undertreatment may cause cardiovascular events or treatment may cause cardiovascular side effects. We found no significant adjusted differences in cardiovascular parameters and neutral results for all cardiovascular outcomes with wide confidence intervals, although all point estimates were favourable for levothyroxine treatment. Therefore, we found no evidence to support any major short to medium term harmful effect on cardiovascular events of levothyroxine treatment for subclinical hypothyroidism in older people, including in those with known prior cardiovascular disease.

Taken together, our finding that treatment with levothyroxine did not change the risk of all cardiovascular outcomes in older adults with SCH is of incremental value to the limited existing literature. We showed that when treatment with levothyroxine is indicated on an individual basis, treatment should not be initiated especially to prevent cardiovascular events, nor should it be withheld because of potential cardiovascular side effects, irrespective of CVD history. Provided that treatment should be carefully monitored and titrated over time, as was in the trials.

Strengths and Limitations

This is a unique combined data analysis of the two largest RCTs to date investigating cardiovascular outcomes in older patients with SCH. Some limitations should be mentioned.

First, it was initially planned in both TRUST and IEMO80+ that cardiovascular events were to be a primary outcome together with thyroid-specific quality of life. Owing to delays

TABLE 1 | Baseline characteristics (n = 842).

Characteristic	No history of CVD		History of CVD	
	Placebo (n = 271)	Levothyroxine (n = 269)	Placebo (n = 151)	Levothyroxine (n = 151)
Age (years), median [IQR]	72.7 [68.6-79.2]	73.6 [68.9-78.8]	79.9 [73.0-84.5]	76.8 [72.0-81.7]
Female sex, n (%)	162 (59.8)	161 (59.9)	62 (41.1)	63 (41.7)
Caucasian[a], n (%)	264 (97.4)	264 (98.1)	150 (99.3)	150 (99.3)
Standard housing[b], n (%)	264 (97.4)	262 (97.4)	142 (94.0)	145 (96.0)
History of cardiovascular disease, n (%)				
Ischemic heart disease[c]			62 (41.1)	63 (41.7)
Stroke or transient ischemic attack			55 (36.4)	33 (21.9)
Peripheral vascular disease			15 (9.9)	20 (13.3)
Revascularisation			46 (30.5)	59 (39.1)
Heart failure			23 (15.2)	15 (9.9)
Atrial fibrillation			53 (35.3)	58 (38.9)
Cardiovascular risk factors, n (%)				
Hypertension	115 (42.8)	133 (49.4)	92 (61.3)	86 (57.0)
Diabetes mellitus	29 (10.7)	40 (14.9)	28 (18.7)	30 (19.9)
Current smoking	25 (9.2)	19 (7.1)	10 (6.6)	13 (8.6)
Former smoking	105 (38.7)	112 (41.6)	76 (50.3)	74 (49.0)
Number of concomitant medicines	3 [1-5]	3 [1-5]	6 [4-6]	6 [4-8]
Clinical parameters				
Body mass index (kg/m^2)	27.2 ± 4.6	27.8 ± 5.2	28.5 ± 4.5	28.5 ± 5.4
Waist circumference (cm)	95.7 ± 12.9	97.1 ± 12.4	100.8 ± 11.4	100.9 ± 12.4
Blood pressure (mmHg)				
Systolic	142 ± 20	143 ± 18	142 ± 20	140 ± 21
Diastolic	75 ± 12	75 ± 11	73 ± 12	72.3 ± 10
Heart rate (beats per min.)	70.4 ± 10.6	69.1 ± 10.6	68.6 ± 13.0	67.6 ± 12.7
Hand-grip strength (kg)	27.3 ± 10.5	27.2 ± 10.3	27.3 ± 11.9	28.5 ± 10.3
Thyroid function[d]				
Thyrotropin (mIU/liter)	6.4 ± 2.1	6.5 ± 2.1	6.2 ± 1.8	6.2 ± 1.7
Median	5.7 [5.1-7.0]	5.7 [5.2-7.0]	5.7 [5.0-6.8]	5.7 [5.0-6.8]
Free thyroxine (pmol/liter)	13.1 ± 1.9	13.4 ± 2.0	14.0 ± 2.0	13.7 ± 2.2
Quality of life[e]				
Hypothyroid Symptoms score	15.4 ± 16.9	17.5 ± 19.2	21.0 ± 20.4	18.9 ± 18.2
Tiredness score	23.0 ± 18.2	25.7 ± 20.7	29.6 ± 22.5	25.5 ± 20.6
EQ-5D descriptive index	0.855 ± 0.18	0.847 ± 0.18	0.804 ± 0.20	0.819 ± 0.22
EQ visual-analogue scale score	77.6 ± 15.9	79.2 ± 15.2	73.3 ± 15.3	76.0 ± 15.1

Values are mean ± standard deviation (SD) or median [interquartile range (IQR)]. Cardiovascular disease (CVD) was defined as ischemic heart disease (both angina pectoris or myocardial infarction), stroke or transient ischemic attack, heart failure, peripheral vascular disease, revascularization or atrial fibrillation. [a]Race was reported by the patient. [b]Standard housing was defined as non-sheltered community accommodation. By contrast, sheltered housing is purpose built grouped housing for older persons, often with an on-site manager or warden. [c]Ischemic heart disease was defined as a history of angina pectoris or previous myocardial infarction. [d] To convert the values for free thyroxine to nanograms per deciliter, divide by 12.87. [e]The Hypothyroid Symptoms score and the Tiredness score from the Thyroid-Related Quality of Life Patient-Reported Outcome (ThyPRO) questionnaire are each assessed on a scale from 0 to 100, with higher scores indicating more symptoms and tiredness, respectively. The minimum clinically important difference for each score has been estimated as 9 points. The EuroQoL [EQ] Group 5-Dimension Self-Report Questionnaire (EQ-5D) scores included both the EQ5D descriptive index (on a scale from –0.59 to 1.00) and the score on the EQ visual-analogue scale (on a scale from 0 to 100); higher scores on each scale indicate better quality of life.

and difficulties in recruitment this was changed as it became apparent that both studies would be underpowered for this aspect (13). However, the studies combined enabled the largest data analysis thus far regarding this subject and it is unlikely that a similar experiment will be successful in the near future, especially not a large one. Overall incidence of cardiovascular outcomes after a median follow-up of 17 months in the patients with SCH was still relatively low, only 44 (5.2%) patients had a fatal or nonfatal cardiovascular event. However, 17 months is still relatively short, and does not exclude a substantial cardiovascular 10-year risk. Second, the limited power hampered us to further stratify according to history of CVD and to distinguish between patients with ischemic heart disease, patients with heart failure or patients with vascular disease elsewhere in the body (e.g. cerebrovascular or peripheral artery disease). Furthermore, of the 252 patients with a history of CVD, only 38 subjects had a history of heart failure. Third, of all included older participants, only 251 (29.8%) defined as the oldest old (≥80 years old). Fourth, mean TSH level was not very high at baseline in the total population (6.4 ± 2.0). Fifth, with respect to ethnicity the study population was predominantly white (98%).

Conclusions

Treatment with levothyroxine did not significantly change the risk of cardiovascular outcomes in older adults with subclinical hypothyroidism, irrespective of a history of CVD.

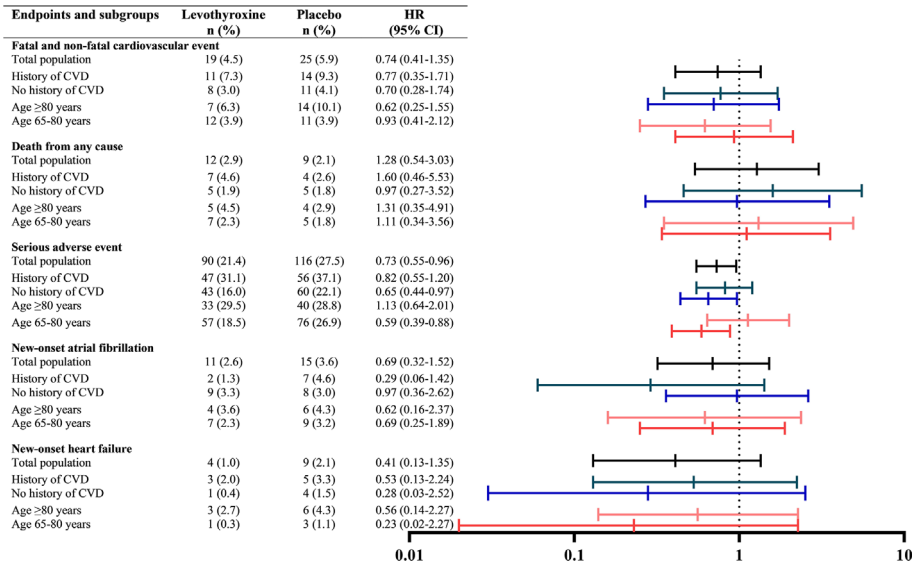

FIGURE 2 | Cardiovascular outcomes stratified for history of cardiovascular disease and age. Cardiovascular disease (CVD) is defined as ischemic heart disease, stroke or transient ischemic attack, heart failure, peripheral vascular disease, revascularisation or atrial fibrillation. Hazard ratios for treatment were obtained from a Cox proportional hazard regression model predicting and were adjusted for study, country, sex and starting dose of levothyroxine.

TABLE 2 | Thyroid function and cardiovascular parameters at 12 months for patients with or without a history of cardiovascular disease*.

Variable	No history of CVD					History of CVD					Interaction
	Baseline		At 12 months			Baseline		At 12 months			
	Placebo (n = 271)	Levothyroxine (n = 269)	Placebo (n = 235)	Levothyroxine (n = 243)	Difference (95% CI)	Placebo (n = 151)	Levothyroxine (n = 151)	Placebo (n = 133)	Levothyroxine (n = 120)	Difference (95% CI)	p-value
Thyrotropin (mIU/L)	6.4 ± 0.1	6.5 ± 0.1	5.6 ± 0.2	3.5 ± 0.1	−2.12 (−2.49 to −1.76)	6.2 ± 0.2	6.2 ± 0.1	5.5 ± 0.2	3.8 ± 0.2	−1.63 (−2.17 to −1.11)	0.31
Median [IQR]	5.8 [5.1 to 7.0]	5.7 [5.2 to 7.0]	4.9 [4.6 to 6.6]	3.2 [2.4 to 4.2]		5.2 [5.0 to 6.8]	5.2 [5.0 to 6.8]	4.9 [3.9 to 6.4]	3.5 [2.7 to 4.4]		
Range	4.6 to 17.6	4.6 to 17.6	0.1 to 46.0	0.03 to 15.9		4.6 to 17.6	4.6 to 14.2	1.9 to 18.0	0.8 to 15.4		
Cardiovascular parameters											
Systolic blood pressure (mm Hg)	142 ± 1.2	143 ± 1.1	139 ± 1.2	140 ± 1.1	0.96 (−1.67 to 3.59)	142 ± 1.6	140 ± 1.7	139 ± 1.7	137 ± 1.9	−1.05 (−5.23 to 3.13)	0.40
Diastolic blood pressure (mm Hg)	75 ± 0.7	75 ± 0.7	74 ± 0.7	74 ± 0.7	0.46 (−1.11 to 2.03)	73 ± 1.0	72 ± 1.0	71 ± 1.1	69 ± 1.2	−1.16 (−3.62 to 1.29)	0.28
Heart rate (beats per minute)	70.4 ± 0.6	69.1 ± 0.6	70.1 ± 0.7	69.3 ± 0.7	1.07(−0.50 to 2.63)	68.6 ± 1.1	67.6 ± 1.0	68.7 ± 1.2	67.2 ± 1.2	−0.78 (−3.12 to 1.56)	0.17
Weight (kg)	74.9 ± 0.9	76.3 ± 0.9	75.0 ± 0.9	76.3 ± 0.9	0.16 (−0.36 to 0.69)	79.3 ± 1.2	80.1 ± 1.4	79.7 ± 1.3	80.6 ± 1.5	0.27 (−0.67 to 1.21)	0.83

*Values are mean ± standard error (SE). CI, confidence interval; CVD, cardiovascular disease. Results at 12 months and between-group differences are adjusted for stratification variables (country, sex, starting dose of levothyroxine and study as random effect) and baseline levels of the same variable with the use of linear mixed models. Between-group differences are the value in the levothyroxine group minus the value in the placebo group. Interaction analyses were performed between treatment and history of CVD and all endpoints. *CVD was defined as ischemic heart disease (both angina pectoris or myocardial infarction), stroke or transient ischemic attack, heart failure, peripheral vascular disease, revascularization or atrial fibrillation.*

DATA AVAILABILITY STATEMENT

Who can access the data: The authors welcome proposals for joint use of the study data after the planned publications of the study data have been completed. Types of analyses: For any purpose, after review and approval from a board of Principle Investigators. Mechanisms of data availability: Data will be made available with investigator support, with a signed data access agreement, after approval of a proposal.

ETHICS STATEMENT

For the UK, the study was approved by the Multicentre Research Ethics Committee (A) and the MHRA, with co-sponsors NHS Greater Glasgow and Clyde and the University of Glasgow. For the Netherlands, the study was approved by the Medical Ethical Committee on Research Involving Human Subjects (CCMO). In Switzerland, the study was approved by the Bern and Lausanne ethical boards and by Swissmedic, the Swiss competent authority for drugs. In Ireland, the study was approved by the Clinical Research Ethics Committee, Cork and by the Health Products Regulatory Authority (formerly known as the Irish Medicines Board). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SM and LZ had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: JJ, RW, PK, OD, NR, TQ, DS, WE, JG, and SM. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: LZ, JJ, and SM. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: LZ. Obtained funding: RW, PK, NR, DS, JG, SM. Administrative, technical, or material support: LZ, JJ, RW, RP, KP, PK, OD, NR, WE, JG, and SM. Study supervision: JJ, RW, OD, NR, JG, and SM. All authors contributed to the article and approved the submitted version.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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