



T4+T3 Combination Therapy: An Unsolved Problem of Increasing Magnitude and Complexity

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Thyroxine (T4)+triiodothyronine (T3) combination therapy can be considered in case of persistent symptoms despite normal serum thyroid stimulating hormone in levothyroxine (LT4)-treated hypothyroid patients. Combination therapy has gained popularity in the last two decades, especially in countries with a relatively high gross domestic product. The prevalence of persistent symptoms has also increased; most frequent are complaints about energy levels and fatigue (80% to 90%), weight management (70% to 75%), memory (60% to 80%), and mood (40% to 50%). Pathophysiological explanations for persistent problems are unrealistic patient expectations, comorbidities, somatic symptoms, related disorders (Diagnostic and Statistical Manual of Mental Disorders [DSM-5]), autoimmune neuroinflammation, and low tissue T3. There is fair circumstantial evidence for the latter cause (tissue and specifically brain T3 content is normalized by T4+T3, not by T4 alone), but the other causes are viewed as more relevant in current practice. This might be related to the ‘hype’ that has emerged surrounding T4+T3 therapy. Although more and better-designed trials are needed to validate the efficacy of T4+T3 combination, the management of persistent symptoms should also be directed towards alternative causes. Improving the doctor-patient relationship and including more and better information is crucial. For example, dissatisfaction with the outcomes of T4 treatment for subclinical hypothyroidism can be anticipated as recent trials have demonstrated that LT4 is hardly effective in improving symptoms associated with subclinical hypothyroidism.

Keywords: Hypothyroidism; T4 monotherapy; T4+T3 combination therapy; Prevalence; Persistent symptoms; Pathophysiology; Management

INTRODUCTION

In 1996, 25 years ago, Escobar-Morreale et al. [1,2] reported that only combined treatment with thyroxine (T4) and triiodothyronine (T3) restored euthyroidism (as judged by normal T4 and T3 tissue contents) simultaneously in all tissues of thyroid-ectomized rats. In 2006, 15 years ago, a meta-analysis of 11 randomized clinical trials performed between 1999 and 2005 was done, comparing T4+T3 combination therapy and T4 monotherapy; it did not find any difference in the outcomes of

both treatment modalities, either in effectiveness or in safety [3]. Furthermore, in 2012, 10 years ago, the European Thyroid Association (ETA) published the first guideline on T4+T3 combination therapy [4].

In the absence of evidence showing superiority of T4+T3 combination therapy, interest in the combination nevertheless continued to grow, specifically because it might potentially resolve persistent symptoms that do occur in 5% to 15% of hypothyroid patients despite treatment with levothyroxine (LT4) and reaching a normal thyroid stimulating hormone (TSH) level

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[5,6]. T4+T3 therapy became rather popular. The 2012 ETA guidelines were specifically offered to enhance safety and to counter indiscriminate use of T4+T3 combination therapy, which “might be considered as an experimental approach in compliant LT4-treated hypothyroid patients who have persistent complaints despite serum TSH values within the reference range, provided they have previously given support to deal with the chronic nature of their disease and associated autoimmune diseases have been ruled out” [4].

What progress has been made in the last decade? Obviously little, as the proportion of dissatisfied patients has increased as well as the number of prescriptions of T4+T3 combination therapy. It remains incompletely understood why a subset of hypothyroid patients on T4 monotherapy has persistent complaints [7]. In this review we will discuss the prevalence of hypothyroidism and its treatment with T4 or T4+T3, as well as the nature and pathophysiology of persistent symptoms on T4 despite a normal TSH. We also propose how to deal with persistent symptoms, including T4+T3 combination therapy. We limit ourselves largely to the literature of the last 5 years, as earlier papers have already been reviewed extensively [8,9].

T4+T3 COMBINATION THERAPY: A QUANTITATIVE APPROACH

Prevalence of overt and subclinical hypothyroidism

Hypothyroidism is a common disease, occurring 5 to 10 times more frequently in women than in men. The global prevalence of overt hypothyroidism in the general population ranges between 0.2% and 5.3% in Europe and 0.3% and 3.7% in the USA (Table 1) [10]. The prevalence figures from the USA originate from population-based surveys and a statewide health fair [11,12]. The European figures are derived from two meta-analyses of published population studies [13,14] and a national survey in Spain [15]. The Japanese data were obtained at a general health check-up [16], and the Korean data come from the sixth Korea National Health and Nutrition Examination Survey [17,18].

Prevalence of treated hypothyroidism

Is there any evidence for increasing prevalence over the last decades? Epidemiological studies in this respect are limited. Most are based on data obtained from drug prescription and hospital discharge databases. The Thyroid Epidemiology Audit and Research Study (TEARS) study from Scotland reported an increase of 63% in the prevalence of treated hypothyroidism in the period 1994–2001 from 3.1% to 5.1% for women and from

Table 1. Prevalence of Undiagnosed Overt and Subclinical Hypothyroidism

Country	Period	Prevalence of overt hypothyroidism, %	Prevalence subclinical hypothyroidism, %
USA [11]	1988–1994	0.3	4.6
USA [12]	1995	0.4	8.5
Europe [13]	1975–2012	0.6	4.6
Europe [14]	2008–2018	0.6	4.1
Spain [15]	2009–2010	0.3	4.6
Japan [16]	2005–2006	0.7	5.8
Korea [17,18]	2013–2015	0.7	3.1

0.5% to 0.9% for men; the year-on-year increase was 7.5% [19]. The National Health and Nutrition Examination Surveys in the USA have described an increase in the use of LT4 from 5.1% in the period 1999–2000 to 6.4% in the period 2011–2012 ($P=0.007$ for trend) [20]. The prevalence of treated hypothyroidism in the Italian region of Piedmont was 3.11% (0.23% for iatrogenic hypothyroidism) in 2012, and in Spain it was 4.2% in 2009 to 2010 [15,21]. In the UK, the prevalence of treated hypothyroidism, based on LT4 prescriptions in a national-level database covering 99% of general practitioner (GP) practices, increased by 57% from 2.3% (1.43 million) in 2005 to 3.5% (2.24 million) in 2014; the year-on-year increase was significant ($P=0.03$) [22]. Growth in population size or prolonged lifespan in the period under investigation only partially explained the observed increase. In multivariate analysis, the prevalence of treated hypothyroidism was positively associated with female sex, white ethnicity and obesity, and negatively with smoking. It was forecasted the prevalence of treated hypothyroidism in 2025 would increase to 4.65% (3.23 million persons) [22]. These data are in accordance with a prevalence of 3.6% for treated hypothyroidism in north-east England in 2016 [23]. A similar trend was observed in the USA, where the proportion of the population reporting thyroid hormone use increased from 4.1% in 1997 to 8.0% in 2016 ($P<0.01$) [24]. This increase occurred predominantly in individuals over age 65. LT4 became the most prescribed drug in the USA in 2014 and was the second most dispensed drug in the UK in 2020 [25,26]. A community-based study in the UK found that the median TSH level at initiation of LT4 therapy fell from 8.7 to 7.9 mU/L between 2001 and 2009 [27]. A Danish study in a primary care population demonstrated a considerable fall in the median serum TSH at LT4 initiation from 10 mU/L in 2001 to 6.8 mU/L in 2015 [28].

Prevalence of T4+T3 combination therapy

The proportion of thyroid hormone users in the Dutch population increased from 1.87% in 2005 to 2.79% in 2011, an increase of 49% [29]. In the same period, the Dutch population size increased only by 2.1%. With regard to the various thyroid hormone preparations, the proportion of only T4 users gradually but consistently decreased from 99.05% in 2005 to 98.98% in 2011. The opposite trend was observed in T4+T3 users, the proportion of which slowly but steadily increased from 0.82% in 2005 to 0.90% in 2011; in absolute numbers, the increase was from 2,499 to 4,179 persons (67%). The proportion of only T3 users remained the same (0.13% and 0.12%). About two-thirds of prescriptions are from GPs and one-third from specialists. In a questionnaire survey among T4+T3 users in Denmark, GPs prescribed the medicine in 44% and specialists in 41% of cases, and 4% of patients bought the drugs through the internet [30]. The serum TSH level at diagnosis was <4, 4–10, 10–20, and >20 mU/L in 21%, 25%, 7%, and 14%, respectively; 32% did not remember. The number of applications for reimbursement of T4+T3 therapy was used as a surrogate for the number of new patients starting T4+T3 therapy. A 3.8-fold increase was observed from 2012 to 2014, obviously induced by the publication of a book describing experience of patients with hypothyroidism and its treatment. A United States survey in 2013 reported that overt hypothyroidism would be treated with LT4 by 99.2% of respondents and that 0.8% would use T4+T3 combination therapy [31]. Persistent hypothyroid symptoms despite achieving a target TSH on LT4 would prompt 3.6% of respondents to use T4+T3 combination therapy. In contrast, a follow-up United States survey in 2017 demonstrated that as many as 18% to 41% of physicians were willing to prescribe T4+T3 combination therapy, depending on the specific scenario [32].

Physicians from North America were found to be more likely to prescribe T4+T3 combination than physicians from outside North America (odds ratio [OR], 1.9; 95% confidence interval [CI], 1.2 to 2.9). A questionnaire survey called Treatment of Hypothyroidism in Europe by Specialists: an International Survey (THESIS) was done recently among members of national endocrine societies in five European countries [33–37]. Although LT4 remained the drug of choice for initiating treatment of hypothyroidism, 1% to 1.5% of respondents already used combined T4+T3 at the initiation of thyroid hormone therapy. Furthermore, 24% to 59% of respondents considered using combination therapy in patients who experience persistent hypothyroid symptoms despite a normal TSH while receiving LT4 (Table 2). Interestingly, this proportion is directly related to a given country's economic health expressed as *per capita* gross domestic product (GDP): the higher the GDP, the higher the willingness to use T4+T3 combination therapy (Fig. 1).

Epicrisis: The overall prevalence of untreated overt and subclinical hypothyroidism is about 0.4% and 4.6%, respectively. The prevalence of treated hypothyroidism has increased in the last two decades, driven largely by the treatment of subclinical hypothyroidism. The prevalence of T4+T3 combination treatment is also on the rise. It is considered more frequently in countries with a high rather than low GDP.

PREVALENCE AND NATURE OF PERSISTENT SYMPTOMS DESPITE A NORMAL TSH ON LT4

In the early 2000s, persistent symptoms despite a normal TSH were reported by 5% to 15% of hypothyroid patients on LT4 treatment [5,6]. One may ask whether these prevalence figures

Table 2. Findings of the THESIS Questionnaire Survey among European Endocrinologists about the Treatment of Hypothyroidism

Country	Responders, n (%)	T4 drug of choice, % ^a	T4+T3 use considered, % ^b	GDP 2019 <i>per capita</i> in \$ (% of world's average) ^c
Italy [33]	797 (39)	99	43	35,614 (282)
Denmark [34]	152 (31)	94	59	65,147 (516)
Romania [35]	316 (42)	99	39	12,131 (96)
Poland [36]	423 (55)	96	32	17,387 (138)
Bulgaria [37]	120 (95)	96	24	9,026 (71)

THESIS, Treatment of Hypothyroidism in Europe by Specialists: an International Survey; T4, thyroxine; T3, triiodothyronine; GDP, gross domestic product.

^aPreference at initiation of thyroid hormone replacement therapy; ^bCombination therapy considered for use in patients with persistent symptoms despite a normal thyroid stimulating hormone on levothyroxine; ^cGDP *per capita* in 2019 in US dollars, with % of world's average GDP in parentheses (<https://data.worldbank.org/indicator/NY.GDP.PCAP.PP.CD>).

changed over the last two decades, and whether more has been learned about the precise nature of these persistent complaints.

The prevalence of persistent symptoms

The prevalence of persistent symptoms has increased according to most respondents of the THESIS survey (Table 3). High prevalence figures are found in countries with a high GDP, whereas the figures are much lower in countries with a low GDP. Approximately one-third of respondents stated that the prevalence of persistent symptoms increased in the last 5 years (Table 4).

The nature of hypothyroid symptoms

The nature of hypothyroid symptoms tends to be non-specific and difficult to distinguish from other conditions or general sub-

optimal health [38]. This was nicely illustrated by a study in patients with newly diagnosed overt autoimmune hypothyroidism using a population-based case-control design [39]. Among 34 symptoms investigated, 13 symptoms were overrepresented in patients with hypothyroidism. Hypothyroid patients suffered mostly from tiredness (81%), dry skin (63%), and shortness of breath (51%). None of the individual symptoms of hypothyroidism had high likelihood ratios or diagnostic ORs [39]. The authors concluded that neither the presence nor absence of any individual hypothyroid symptom had sufficient accuracy for establishing the diagnosis of hypothyroidism.

A Danish internet-based questionnaire study inquired about persistent symptoms on LT4 therapy before the initiation of T4+T3 combination therapy [30]. The median number of symptoms per participant was 7 (interquartile range [IQR], 5 to 8); as many as 69% of patients had ≥ 6 different symptoms. The frequency of these symptoms is listed in Table 5. An online survey of hypothyroid patients, posted on the American Thyroid Association website, asked the question. If you are not satisfied, indi-

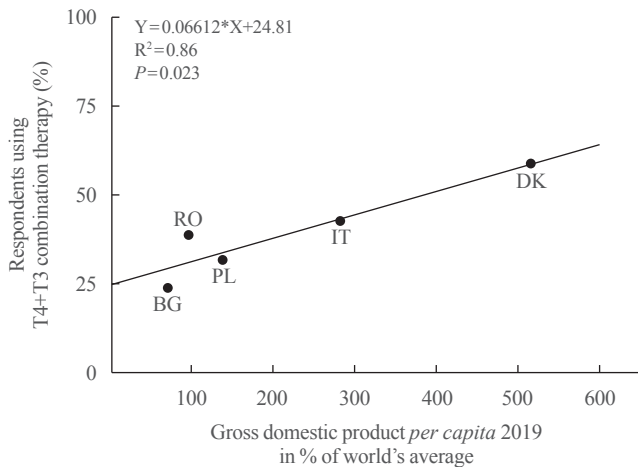


Fig. 1. Relationship between the proportion of respondents willing to use thyroxine (T4)+triiodothyronine (T3) combination therapy in five European countries in patients with persistent symptoms despite a normal thyroid stimulating hormone on levothyroxine, and their annual *per capita* gross domestic product (GDP) in 2019 given as percentage of the world's average. BG, Bulgaria [37]; RO, Romania [35]; PL, Poland [36]; IT, Italy [33]; DK, Denmark [34].

Table 4. Changes in the Frequency of Persistent Symptoms Despite a Normal TSH in the Last 5 Years as Estimated by European Endocrinologists Responding to the THESIS Questionnaire

Country	Changes in frequency of persistent symptoms despite a normal TSH over the last 5 years as estimated by respondents			
	Increase last 5 yr, %	No change last 5 yr, %	Decrease last 5 yr, %	Not sure, %
Denmark [34]	58.6	13.8	6.6	21.1
Romania [35]	-	31.8	24.1	-
Poland [36]	36.4	28.1	-	-
Bulgaria [37]	26.6	35.0	14.2	24.2

TSH, thyroid stimulating hormone; THESIS, Treatment of Hypothyroidism in Europe by Specialists: an International Survey.

Table 3. Frequency of Persistent Symptoms Despite a Normal TSH in LT4-Treated Hypothyroid Patients as Estimated by European Endocrinologists Responding to the THESIS Questionnaire

Country	Frequency of persistent symptoms as estimated by respondents, %				
	<5%	6%–10%	11%–30%	>30%	Not sure
Denmark [34]	23.0	37.5	1.3	11.2	27
Romania [35]	46.9	37.9	-	-	-
Poland [36]	33.1	28.8	-	-	-
Bulgaria [37]	41.7	34.2	6.6	2.5	15

TSH, thyroid stimulating hormone; LT4, levothyroxine; THESIS, Treatment of Hypothyroidism in Europe by Specialists: an International Survey.

Table 5. Frequency of Different Symptoms on LT4 Monotherapy before Initiating T4+T3 Combination Therapy among 293 Responders to a Danish Internet-Based Questionnaire Study [30]

Symptom	Main symptom, %	Prevalence, %
Being tired	27	91
Lack of energy	17	87
Cognitive problems	11	83
Musculoskeletal symptoms	10	76
Weight problems	8	75
Pain	4	49
Diffuse symptoms	4	48
Depression	2	39
Constipation	2	42
Sweating	0.3	31
Other	15	36

LT4, levothyroxine; T4, thyroxine; T3, triiodothyronine.

cate relevant areas you feel are affected by your thyroid treatment with LT4? [40]. The four most prevalent answers among 6,949 respondents were fatigue or energy levels (80%), weight management (70%), memory (60%), and mood (49%). These prevalence figures are in good agreement with those from the Danish online survey (Table 5) [30]. The issue of body weight might be relevant, as the preference for T4+T3 combination therapy in some of the early randomized controlled trials (RCTs) could be linked to greater weight loss [8]. In an open-label cohort study, 23 hypothyroid patients referred because of persistent symptoms despite adequate LT4 monotherapy were switched to T4+T3 combination therapy at a dose ratio of 1:1 [41]. Quality of life (QoL) assessed by the Thypro-39 composite score improved (from a baseline value of 54 towards 15 and 20 after 3 and 12 months, respectively), but there was no change in body weight. In a meta-analysis of seven blinded RCTs, the pooled prevalence rate for preference of combination therapy was 46.2% [42]. Sensitivity analysis explained the preference for T4+T3 combination in part by treatment effects on serum TSH, mood and symptoms, but not on QoL or body weight. There existed a positive association between the total daily liothyronine (LT3) dose and treatment preference [42].

Prominent dissatisfaction

Prominent dissatisfaction among 12,146 treated hypothyroid patients, measured on a scale from 1 (not satisfied) to 10 (very satisfied), was observed in a United States online survey done in 2017 [40]. Satisfaction was lowest in the LT4 group (median

score 5; IQR, 3 to 7), intermediate in the T4+T3 group (median score 6; IQR, 3 to 8), and highest in the desiccated thyroid extract (DTE) group (median score 7; IQR, 5 to 9). Respondents taking DTE compared to those taking T4 or T4+T3 were less likely to report problems with fatigue/energy levels (−10% and −9%, respectively), weight management (−5% and −7%), mood (−11% and −11%), and memory (−8% and −11%) (all *P* values <0.0001). It should be emphasized that this online survey among treated hypothyroid patients was based on responses from a self-selected sample, unlikely to represent the whole United States population of hypothyroid patients, and therefore liable to multiple biases [40]. The online survey captured predominantly women, half of the respondents had changed their physician twice or more, and two-thirds believed that stress or physical comorbidities other than hypothyroidism might have caused at least part of the symptoms [40]. Similar restrictions apply to another online survey of people with treated hypothyroidism in the UK in 2019 [43]. Immediately after posting the questionnaire on the website, there was a surge of responses and the maximum number of responses allowed by the license (*n*=1,014) was reached within 24 hours. The sample thus represented about 0.04% of all hypothyroid patients in the UK, and was liable to bias. Satisfaction with treatment and care was recorded as a binary response (satisfied or not satisfied), and QoL was recorded on a scale of 0 to 100 (0 being worst and 100 being best) [43]. The proportion of dissatisfaction in patients treated with DTE (*n*=123), LT4 (*n*=677), and T4+T3 (*n*=124) was 83%, 78%, and 69%, respectively; the mean corresponding QoL was 54, 46, and 56. Multivariate analysis showed significant positive correlations between satisfaction and age, male gender, currently being under the care of a thyroid specialist, GP-prescribed DTE or T4+T3, and being fully informed by one's GP; significant negative correlations existed between satisfaction and expectation for more support from one's GP, negative experiences with LT4, the expectation that LT4 would resolve all symptoms, and the expectation to be referred to a specialist. QoL was positively correlated with male gender and duration of hypothyroidism, and was negatively correlated with age, ≥3 visits to a GP with symptoms of hypothyroidism before diagnosis, obtaining treatment with DTE, T4+T3, or T3 without the GP's help, experiencing difficulties with LT4, the expectation that LT4 would resolve all symptoms, and the expectation for more support from GP. It is surprising to find that the level of satisfaction and QoL were not substantially different between users of LT4, T4+T3, and DTE, suggesting that other determinants than the thyroid hormone preparation must play a role.

The authors conclude that focusing on enhancing the patient experience and clarifying expectations at diagnosis may improve satisfaction and QoL [43].

Epicrisis: The prevalence of persistent symptoms in LT4-treated hypothyroid patients despite a normal TSH has increased in the past 20 years, especially in countries with a high *per capita* GDP. The median number of persistent symptoms per patient is 7 (IQR, 5 to 8), and two-thirds of patients have ≥ 6 different symptoms. The four most prevalent areas of persistent complaints regard fatigue or energy levels (80% to 90%), weight management (70% to 75%), memory (60% to 80%), and mood (40% to 50%). Satisfaction with the received treatment for hypothyroidism was lowest for T4, intermediate for T4+T3, and highest for DTE in an online United States survey among patients, but in an online UK survey, satisfaction rates were not substantially different between the various thyroid hormone preparations, although QoL was lower in T4 patients than in T4+T3 or DTE patients. Both online surveys were prone to bias.

PATHOPHYSIOLOGICAL EXPLANATIONS FOR PERSISTENT SYMPTOMS ON LT4

Endocrinologists from four European countries answered questions in the THESIS survey on what they considered the most likely or unlikely cause of persistent symptoms in LT4-treated patients with a normal TSH [34-37]. Their answers are listed in Table 6. They could choose from eight different causes. It is remarkable to see how much agreement exists among these physicians from different countries. One may assume strong agreement about a particular cause if the range of respondents who (strongly) agree about a particular cause does not overlap with the range of respondents who (strongly) disagree with that particular cause. Applying this assumption, it is clear that the inability of LT4 to restore physiological function is viewed as an unlikely cause of persistent symptoms, whereas psychosocial factors, comorbidities, unrealistic expectations, and the burden of chronic disease are considered to be more likely causes. Chronic fatigue syndrome and the burden of having to take medication are also viewed—but less strongly—as likely explanations, whereas respondents are divided about the role of inflammation due to autoimmunity.

Low tissue T3

The inability of LT4 to restore thyroid hormone physiology is aptly called the “low tissue T3 hypothesis” by Perros et al. [44]. The name directly refers to the basic research by Escobar-Mor-

Table 6. Frequency of Possible Causes for Persistent Symptoms Despite a Normal TSH level in LT4-Treated Hypothyroid Patients, as Perceived by European Endocrinologists Responding to the THESIS Questionnaire^a

Possible cause of persistent symptoms despite a normal TSH on LT4	Proportion of respondents ^b	
	(Strongly) agree, %	(Strongly) disagree, %
Inability of LT4 to restore physiology	12–20	53–63
Psychosocial factors	67–82	3–14
Comorbidities	42–85	5–16
Chronic fatigue syndrome	24–77	7–21
Patient unrealistic expectation	58–72	6–19
Inflammation due to autoimmunity	15–48	20–41
Burden of chronic disease	40–85	2–24
Burden of having to take medication	30–44	15–26

TSH, thyroid stimulating hormone; LT4, levothyroxine; THESIS, Treatment of Hypothyroidism in Europe by Specialists: an International Survey.

^aRespondents from Denmark [34], Romania [35], Poland [36], and Bulgaria [37]; ^bFigures indicate range (lowest %–highest %) of respondents' answers.

reale et al. [1,2], demonstrating in experimental animals that tissue T3 content could be normalized only by the combined administration of T4 and T3, not by T4 alone. There is extensive circumstantial evidence supporting this hypothesis. Hypothyroid patients replaced with LT4 require somewhat higher serum free thyroxine (FT4) levels in order to normalize serum TSH, whereas their serum free triiodothyronine (FT3) levels are somewhat lower than in euthyroid controls. Actually, 7.2% of hypothyroid patients on LT4 have FT4 levels above the upper normal limit, and 15.2% of patients have FT3 levels below the lower normal limit [45]. To compensate for the reduced thyroidal secretion of T3 (normally responsible for 20% of the daily T3 production), more T3 must be generated in extrathyroidal tissues from exogenous T4. Some tissues depend largely on serum T3 for their T3 content, whereas other tissues are capable of producing T3 themselves by deiodination of local T4. Three types of deiodinases regulate the conversion of T4 into T3 and the inactivation of T4 and T3. The expression of these enzymes varies between tissues, and it has been suggested that a polymorphism in the deiodinase 2 gene (Thr92Ala) may cause slight changes in deiodinase activity but important changes in thyroid hormone bioavailability [38]. Indeed, carriers of the Thr92Ala polymorphism demonstrate a hypothyroid-like state in the brain [46]. The co-existence of polymorphisms in the iodothyronine

deiodinase 2 (*DIO2*) gene (rs225014=Thr92Ala) and the thyroid hormone transporter gene monocarboxylate transporter 10 (*MCT10*; rs17606253) significantly enhanced the preference for T4+T3 combination therapy (the preferences in patients with 0, 1, or 2 polymorphisms were 42%, 63%, and 100% respectively) [47]. In a study evaluating tissue function tests before total thyroidectomy and at 1 year postoperatively when using LT4, it was found that peripheral tissue function tests indicated mild hyperthyroidism at TSH <0.03 mU/L and mild hypothyroidism at TSH 0.3 to 5.0 mU/L; the tissues were closest to euthyroidism at TSH 0.03 to 0.3 mU/L [48]. A normal serum TSH level consequently does not necessarily indicate a euthyroid state at the tissue level [49]. In accordance, a systematic review found that clinical parameters are associated with FT4 or FT3 significantly more often than with TSH levels (50% and 23% respectively, $P < 0.0001$) [50]. The scientific basis of the “low tissue T3 hypothesis” is thus sound, and individualized therapy for hypothyroidism could be indicated, as LT4 monotherapy may provide dissatisfaction in a subset of patients [7].

The most remarkable finding in the questionnaire survey is that the majority of respondents disagreed that the “low tissue T3 hypothesis” plays a major causal role in persistent complaints. My feeling is that 10 years ago, it was the opposite and most specialists supported this hypothesis as a reasonable explanation of persistent symptoms. If so, what changed the perception of doctors that other factors must be involved? The very idea that there existed an alternative for T4 monotherapy became well known among hypothyroid patients, thanks to information by active thyroid patient associations in many countries and improved counseling by physicians, boosted by ongoing scientific reports that apparently strengthened the rationale for combination treatment. T4+T3 therapy became thus rather popular, and attractive to dissatisfied patients. It is against this background that the observed direct relationship between the use of T4+T3 and the *per capita* GDP should be considered. People in richer countries have more time and resources at their disposal to deal with their health problems, and can afford to buy the pills required for the T4+T3 combination treatment, which are not always available or reimbursed by insurance companies.

Unrealistic expectations

The persistence of symptoms despite ‘adequate’ LT4 monotherapy may generate dissatisfaction in patients; these patients could have great expectations about the outcomes, and could be inclined to believe it will resolve all their symptoms [43]. Epidemiological data (summarized above) demonstrate most patients

treated with LT4 in the last two decades had subclinical hypothyroidism (their median TSH before treatment was 6.8 to 7.9 mU/L). A large placebo-controlled trial among patients with subclinical hypothyroidism at least 65 years of age demonstrated no apparent benefits of LT4 treatment [51]. A meta-analysis among nonpregnant adults with subclinical hypothyroidism showed the use of thyroid hormone therapy was not associated with improvements in general QoL or thyroid-related symptoms [52]. Later studies among adults aged 80 years and older with subclinical hypothyroidism confirmed that LT4 treatment, compared to placebo, was not significantly associated with improvement in hypothyroid symptoms, fatigue, or depressive symptoms [53,54]. A guideline panel including patients, clinicians, and methodologists issued in 2019 a strong recommendation against thyroid hormones in adults with subclinical hypothyroidism (which may not apply to pregnant women, patients with TSH >20 mU/L, patients with severe symptoms, or young adults ≤30 years of age) [55]. Furthermore, 36% of patients with treated subclinical hypothyroidism remain euthyroid after thyroid hormone discontinuation [56]. It is thus likely that most patients who were dissatisfied with the outcome of LT4 treatment had received LT4 because of subclinical hypothyroidism, a condition that by itself poorly responds to LT4.

Comorbidities

Associated autoimmune diseases occur in 14% of patients with Hashimoto’s disease and in 10% of patients with Graves’ disease [57]. Therefore the 2012 ETA guidelines already recommended excluding these comorbidities before embarking on T4+T3 combination therapy [4]. Symptoms resembling those of hypothyroidism also occur in medical conditions like chronic fatigue, anemia, stress, and changes in body weight [38]. It would be prudent to check for such conditions unrelated to the thyroid gland itself. The issue of body weight deserves special attention, as the responses to the THESIS survey disclose the use of LT4 in obese patients [33-37]. Serum TSH is significantly higher in obese patients than in normal weight controls; subclinical hypothyroidism is recorded in 13.7% of obese patients, but thyroid autoimmunity is not a major cause [58-60]. Longitudinal studies suggest that changes in the hypothalamus-pituitary-thyroid axis are side effects of increasing body weight rather than its cause, and are reduced after weight loss obtained by caloric restriction [61]. The increase in serum TSH in the absence of thyroid antibodies is likely an adaptive response. Recent European Society of Endocrinology guidelines recommend testing all patients with obesity for hypothyroidism, based on

TSH; if TSH is elevated (using the same reference range as for non-obese), FT4 and thyroid peroxidase antibody (TPO-Ab) should be measured [62]. The guidelines recommend against the use of thyroid hormones to treat obesity in case of normal thyroid function; they also recommend that hyperthyrotropinemia (elevated TSH and normal FT4) should not be treated in obesity with the aim of reducing body weight.

Burden of chronic disease and burden of having to take medication

The awareness of having a chronic disease and lifelong dependency on thyroid medication could make patients unhappy and less healthy [4,9]. Patients with persistent symptoms despite a normal serum TSH level frequently feel that their normal TSH presents a barrier to further evaluation. GPs and nurses often have inadequate knowledge of medication interactions and LT4 pharmacokinetics; information exchange is usually restricted by time and often centered on symptoms rather than patient education [63]. Positive correlations were noticed between satisfaction and being well-informed about hypothyroidism, whereas negative correlations were observed between satisfaction and expectations for more support from one's GP [43]. Improvement of the interactions between physicians and patients could reduce barriers to optimal thyroid replacement [9].

Somatic symptom and related disorders

Up to 85% of respondents in the THESIS survey thought that psychosocial factors and chronic fatigue syndrome can play a causal role in persistent symptoms. These patients may have somatic symptom and related disorders (SSRD) as proposed by Perros et al. [44]. SSRD is a diagnostic classification with specific criteria described in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [64,65]. It refers to persistent bodily symptoms associated with significant functional impairment, psychological distress, and high healthcare costs. The distress can concern bodily symptoms in the context of a chronic medical condition, such as hypothyroidism, or medically unexplained symptoms. It can be accompanied by anxiety or depressive disorders [44]. An individual with SSRD has a maladaptive reaction to a somatic symptom [66]. Perros et al. [44] elegantly describe the sequence of affairs: "Patients with SSRD have multiple medical consultations and inevitably thyroid function tests are ordered." "Approximately 10% of SSRD patients may also have thyroid dysfunction, usually subclinical hypothyroidism. If patient and doctor assume the symptoms are due to hypothyroidism, LT4 is prescribed but will not be followed by

symptom resolution if the actual diagnosis is SSRD. Any benefits tend to be minor and transient, leading to escalation of the dose of LT4, without consistent symptomatic improvement." "LT4 is declared ineffective by the patient who, having consulted blogs and patient forums, may then seek treatment with T4+T3 or DTE. The patient may encounter resistance from the doctor to prescribe these treatments leading to consultations with several specialists or alternative practitioners or purchasing LT3 or DTE online. The difficulty that patients experience accessing their 'desired' treatment may also increase the perception of a benefit of treatment when they receive it, although symptoms usually persist. Frustration and dissatisfaction ensue and are perpetuated by the absence of effective treatment directed at the underlying cause of the symptoms."

Inflammation due to autoimmunity

A cross-sectional study among patients with autoimmune hypothyroidism observed that TPO-Ab levels (but not TSH, FT4, or FT3) are related to goiter symptoms, depressivity, and anxiety [67]. A meta-analysis observed an association between autoimmune thyroiditis and depression (OR, 3.56; 95% CI, 2.14 to 5.94) or anxiety (OR, 2.32; 95% CI, 1.40 to 3.85) [68]. LT4-treated patients with persistent symptoms despite a normal TSH and high TPO-Ab were randomized to receive total thyroidectomy or continuation of LT4 treatment; QoL and fatigue improved after total thyroidectomy. After 1.5 years, median TPO-Ab values were reduced from 2,232 to 152 kU/L in the surgical group, and from 2,052 to 1,300 kU/L in the medical group [69]. The autoimmune neuroinflammation hypothesis is the only cause of persistent symptoms shown in Table 5, for which there existed a complete overlap between respondents agreeing or not agreeing with this particular cause (Table 5). Obviously, respondents felt quite uncertain about this cause. However, the hypothesis remains plausible, as strengthened by a recent systematic review [70].

Epicrisis: Persistent symptoms in LT4-treated patients despite a normal TSH can have several causes. Whereas the "low tissue T3" hypothesis was dominant a decade ago, nowadays many other causes are thought to be likely involved including unrealistic patient expectations, comorbidities, and the SSRD hypothesis. The multifactorial nature of persistent symptoms has evolved against the background of "hype" surrounding T4+T3 combination treatment in many countries ("hype" is something that, especially thanks to efforts of the media, emerges as a fashion or sensation in a specific public).

HOW TO MAKE PROGRESS IN THE MANAGEMENT OF PERSISTENT SYMPTOMS ON LT4 DESPITE A NORMAL TSH?

The diversity of causes for persistent symptoms should be taken into account in the management plan.

Mitigate unrealistic expectations

Can the occurrence of persistent symptoms on LT4 treatment be avoided? Probably so, at least to a certain extent, especially in patients who had unrealistic expectations about the outcome of LT4 treatment. We have seen an increase in the prevalence of treated hypothyroidism in the last decades, mostly due to an increase in the prevalence of treated subclinical hypothyroidism [27,28]. More recently, it has become clear from placebo-controlled RCTs that the use of thyroid hormone in subclinical hypothyroidism is not associated with improvements in QoL or thyroid-related symptoms [52]. Better counseling of patients and more information on what might be expected from treatment before initiating LT4, might reduce unrealistic expectations and the chance of persisting symptoms.

Check for comorbidities

Persistent symptoms are sometimes caused by associated autoimmune diseases, which in view of their high prevalence in Hashimoto's thyroiditis (13.7%) should be given more attention [57]. The rising worldwide prevalence of obesity is of concern in this context, because 14% of obese patients have subclinical hypothyroidism, often without thyroid antibodies [58-60]. Recent guidelines recommend not to treat isolated hyperthyrotropinemia in obese patients with thyroid hormone if the goal of treatment is reduction of body weight [62]. This advice will prevent dissatisfaction with the outcome of LT4 treatment, as a recent meta-analysis showed that treatment of subclinical hypothyroidism does not improve clinical symptoms such as overweight [52].

Improve doctor-patient relationship

Many studies report that dissatisfaction with LT4 outcomes in hypothyroid patients is related to previous negative experiences with health care workers [32,38,40,43,44]. For instance, dissatisfied patients had often paid ≥ 3 visits to their GP with symptoms before the diagnosis of hypothyroidism was made, had changed their GP ≥ 2 times, were not fully informed or had expected more support from their doctor. Doctors are instrumental in helping patients to cope with the burden of having a chronic disease and the burden of taking daily medication. Focusing on

enhancing the patient experience and clarifying expectations at diagnosis may improve satisfaction and QoL [43].

Explore cognitive behavioral therapy and a collaborative care model

Hypothyroid women on LT4 (score < 60 on the SF36 QoL questionnaire) were randomized to cognitive behavioral therapy (CBT) (8 weekly sessions each lasting 90 minutes, in a group of 12) or no specific intervention; CBT improved scores for emotional health, energy, and general health to a greater extent than in controls [71]. CBT might be feasible as treatment for somatic symptom disorder [72], and recommendations have been published for core outcome domains in clinical trials on somatic symptom disorder [73]. A collaborative care model combining training with psychiatric consultation in the general practice setting could also be an effective intervention in the treatment of persistent medically unexplained symptoms [74]. It is obvious that much has to be learned about this approach to persistent symptoms in LT4-treated hypothyroid patients.

Consider T4+T3 combination therapy

To validate the "low tissue T3" hypothesis, more and better-designed RCTs should be done. The RCTs carried out so far did not provide conclusive answers, as most if not all studies could be criticized for the following reasons: (1) heterogeneous patient population including hypothyroid patients due to Hashimoto's disease or thyroidectomy/ ^{131}I therapy (for thyroid cancer, multinodular goiter, or Graves' disease); (2) inclusion of patients irrespective of persistent symptoms; (3) too small a sample size; (4) wide variation in T4+T3 dosages in combination treatment; and (5) different primary and secondary outcomes [8,9]. To promote discussions about an optimal study design, the American, European and British thyroid associations have recently published a consensus document, which is very helpful [75]. My own recommendations for a new RCT comparing T4 monotherapy versus T4+T3 combination therapy would be:

(1) Use more strict selection criteria: The study should include hypothyroid patients on a stable dose of LT4 for at least 6 months, with persistent symptoms and a normal serum TSH level, in whom associated autoimmune comorbidities have been ruled out. I would exclude patients who initially were treated because of subclinical hypothyroidism, as treatment is unlikely to improve their symptoms [52]. This probably means excluding patients who used $< 1.2 \mu\text{g}/\text{kg}/\text{day}$ LT4 as recommended by the consensus panel [75].

(2) Choose a randomized, double-blind, parallel study design:

The double-blind design should be ensured by having placebo pills besides the LT4 pills in the T4 monotherapy arm. A cross-over study design has the inherent risk of a carry-over effect. The duration of the intervention should be sufficiently long (≥ 6 months), because we do not know how long it will take before tissue T3 content is normalized.

(3) Calculate the sample size: It should be high enough to allow a subanalysis between carriers of specific polymorphisms (e.g., *DIO2*, *MCT8*, *MCT10*, *OATP1C1*) and noncarriers [76, 77]. One should therefore know the prevalence of these polymorphisms. The Ala/Ala genotype of the *DIO2* Thr92Ala polymorphism is present in 11% of both LT4 users and the general population, although without effects on differences in thyroid hormone parameters, health-related QoL, and cognitive functioning [78]. It could be difficult to achieve the required large sample size. In Norwegian women in the period from 1995–1997 to 2006–2008, the prevalence of untreated overt hypothyroidism decreased by 84% (from 0.75% to 0.16%) and that of untreated subclinical hypothyroidism decreased by 64% (from 3.0% to 1.1%), whereas that of treated hypothyroidism increased by 60% (from 5.0% to 8.0%); the prevalence of any form of hypothyroidism remained essentially similar (9% in women and 3% in men) [79].

(4) Calculate T4 and T3 dosages of combination treatment: This is a controversial area. Consensus exists that the daily T3 dose should be split into two administrations (as long as a slow-release T3 preparation is not available). Some physicians just replace part of the usual T4 dose by T3 at a substitution ratio of 3:1 (e.g., 25 μg of T4 is replaced by 7.5 μg of T3) [80]. A daily dose of 150 μg of T4 during monotherapy would thus be transferred into 125 μg of T4+7.5 μg of T3 during combination therapy (i.e., a dose ratio of 17:1). I prefer this dose ratio, which is closest to the physiological T4 to T3 secretion ratio of 16:1 by the thyroid gland itself [81]. Most studies in the literature used lower T4:T3 dose ratios, in the order of 5:1 to 10:1, which might be more effective but also liable to more side effects [1]. Adaptation of the combination dosage should be considered if serum TSH values are encountered outside the reference range. It makes sense not to change T4 and T3 doses simultaneously; the ETA guidelines recommend to adapt first the daily T3 dose [1]. Maintenance of a normal serum TSH level is prudent because two large independent population studies over the past 2 years have shown that mortality of hypothyroid patients treated with LT4 is increased when the serum TSH exceeds or is reduced outside the normal reference range [82]. Residual thyroid function (RTF) might be a key factor in the success of combination

therapy. A recent algorithm estimates RTF and then optimizes T4+T3 dosages, resulting in T4:T3 dose ratios of 8:1 to 13:1 with escalating RTF [83].

(5) Define primary and secondary outcomes: It would be advantageous if RCTs would use the same primary outcome. A suitable candidate is the thyroid-specific and well-validated QoL questionnaire, the ThyPRO [84]. This patient-reported outcome instrument consists of 84 items summarized in 13 scales; each item is rated on a 0–4 Likert scale to yield thirteen 0–100 scales, with higher scores indicating worse health status. The scores for each scale are nicely visualized on a ThyPRO radar plot. The ThyPRO has good cross-cultural validity; the shortened ThyPRO-39, which is now available in many languages, might be preferred [41,85]. A secondary outcome should be patient preference for monotherapy or combination therapy. A variety of biologic markers, including metabolic, cardiovascular, cognitive, and musculoskeletal parameters, can also be recorded.

(6) Incorporate safety precautions: Hyperthyroid symptoms, tachycardia, atrial fibrillation, and decreased bone density and fractures would all be relevant, and should be assessed [75]. Fortunately, it is possible using T4+T3 combination therapy to keep serum TSH, FT4, and FT3 within their normal range in $\geq 90\%$ of patients [86]. Observational studies lasting 9 to 17 years found no increased risk of cardiovascular disease, atrial fibrillation, or fractures in patients using T3 compared to patients using T4 [87,88]. The use of LT3 did not lead to increased breast cancer or any cancer incidence and mortality compared with LT4 use [89]. There was only an increased incident use of antipsychotic medication during follow-up in T3 users [87].

Epicrisis: Improving the doctor-patient relationship seems most relevant, besides mitigating unrealistic expectations and looking for comorbidities. CBT is promising in patients with somatic symptom disorder. To validate the “low tissue T3” hypothesis, there is no alternative but to conduct more and better-designed RCTs comparing T4+T3 combination therapy and T4 monotherapy. The 2012 ETA guidelines for individual T4+T3 treatment are still well-grounded.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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