A Questionnaire Survey of German Thyroidologists on the Use of Thyroid Hormones in Hypothyroid and Euthyroid Patients: The THESIS (Treatment of Hypothyroidism in Europe by Specialists: An International Survey) Collaborative

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ABSTRACT

Objective To identify the attitudes of German thyroid specialists towards the clinical treatment of hypothyroidism using thyroid hormones (TH).

Methods All members of the thyroid section of the German Endocrine Society (DGE) were e-mailed an invitation to participate in a web-based survey about substitution with TH.

Results Out of 206 members of the DGE's thyroid section, 163 (79.1 %) responses were received and included in the analysis. Of responding members, 98.6 % used levothyroxine (LT4) as the treatment of choice, and 45.4 % also prescribed combination therapy with liothyronine (LT4 + LT3) in their clinical practice ($p < 0.001$). LT4 + LT3 combination was favored in patients with persistent hypothyroidism symptoms despite biochemical euthyroidism on LT4 treatment ($p < 0.001$). Of all respondents, 26.4 % never indicated TH therapy for euthyroid patients ($p < 0.001$), while the remainder would consider THs for one or more indications (62.9 % for euthyroid infertile women with high anti-thyroid antibody levels ($p < 0.001$), 7.1 % in patients with severe hypercholesterolemia, as complementary treatment ($p = 0.007$), and 57.1 % in patients with simple goiter ($p < 0.001$)). In conditions that could interfere with LT4 absorption, most respondents still preferred tablets and did not

expect a significant difference when switching from one LT4 formulation to another.

Conclusion For German thyroid specialists, LT4 is the treatment of choice for hypothyroidism. Combination therapy with LT4 + LT3 was considered for patients with persistent symptoms. Even in conditions that could affect bioavailability, German thyroid specialists prefer LT4 tablets rather than other LT4 formulations, such as liquid or soft-gel capsules. The widespread use of thyroid hormone for non-hypothyroid conditions is not consistent with current evidence and needs further study.

Introduction

Hypothyroidism, either overt or subclinical, affects approximately 3 % of the European population [1]. Levothyroxine (LT4) is the standard therapy for thyroid hormone (TH) substitution, and different types of LT4 formulations are available, including tablets, liquid solutions, and soft-gel capsules, in several European countries. Liquid solutions and soft-gel capsules are relatively new LT4 formulations and were produced to overcome some of the bioavailability issues with tablets [2]. Oral LT4 bioavailability may be reduced when tablets are administered simultaneously with beverages, food, other types of medications (e. g., calcium carbonate, phosphate binders, proton-pump inhibitors, and iron supplements), or in patients with concurrent gastrointestinal conditions (e. g., atrophic gastritis, coeliac disease, *Helicobacter pylori* infection, and bariatric surgery) [2, 3].

Although all available LT4 formulations are regarded as effective in treating hypothyroidism, pre-existing morbidity may be increased in hypothyroid individuals, and post-diagnosis co-morbidity due to psychiatric [4] and somatic [5] disorders is higher than in euthyroid controls. This is associated with a higher rate of disability pension, excess mortality from natural and unnatural causes [6, 7], and loss of labor market income compared to the background population [8]. The aforementioned, together with the fact that quality of life is not fully restored [9, 10] in a significant proportion of patients, is one of several reasons for a continued pursuit to optimize TH substitution in hypothyroid individuals. Differences in bioavailability in favor of soft-gel capsules and liquid solution compared to tablets have been suggested in both patients with and without impaired absorption [3]. However liquid solution and soft-gel capsules are more expensive than tablets, and the cost-effectiveness of switching from tablets to the new formulations remains mostly based on limited size and uncontrolled studies [11].

Before LT4 was synthesized, desiccated thyroid extract (DTE) was the standard therapy for hypothyroidism. DTE is derived from the thyroid glands of animals, primarily pigs, and contains both T4 and T3. Combination therapy can also be administered to patients using the synthetic preparation of T3, liothyronine (LT3), and LT4. Thyroid guidelines uniformly favor LT4 as standard therapy [12]; however, some patients with thyroid failure have persistent symptoms despite adequate thyroid hormone replacement therapy with LT4 [9]. According to international guidelines and a recent European and American consensus document, combination therapy with LT4 and LT3 may be considered in such individuals, mostly as a short treatment trial [13, 14].

Over the last decade, LT4 prescriptions have been increasing in several European countries [15, 16]. This can probably be explained by changing clinical practices, particularly a decreasing thyroid stimulating hormone (TSH) threshold for initiating treatment [17] and increasing the use of biochemical tests [18, 19]. Furthermore, combination therapy with LT4 + LT3 or DTE is also gaining attention [17], mostly due to growing demands from patients dissatisfied with the LT4 treatment [20, 21]. However, prescribing T3-containing preparations is not without risks. Side effects, including excess morbidity [22, 23] and mortality [24], due to possible factitious hyperthyroidism are a concern, and the broad evidence for non-superiority of combination therapy over LT4 does not support this trend [12].

In Germany, where iodine fortification of table salt is voluntary, the iodine supply improved in the early 2000s but declined later [25]. Germany is thus, again, a country with borderline iodine status and about 30 % of the adult population are iodine deficient [26]. The health insurance system in Germany consists of a mixed, private and public sector. Most German patients with hypothyroidism are treated by family doctors/general practitioners. Patients referred to endocrinologists include cases with complicated hypothyroidism and those with other concomitant endocrine disorders. LT4 tablets, LT3 tablets, LT4 + LT3 combination tablets, LT4-soft-gel capsules, and LT4 liquid solution are commercially available in Germany, without prescribing restrictions. This survey was part of an international initiative referred to as THESIS (*T*reatment of *H*ypothyroidism in *E*urope by *S*pecialists: An *I*nternational *S*urvey). We aimed to investigate the use of TH for hypothyroid and euthyroid patients by German thyroidologists and hence asked members of the thyroid section of the German Society for Endocrinology (DGE) for their opinion and personal experience on this issue.

Materials and Methods

The questionnaire was developed to evaluate the attitude of European thyroidologists regarding the treatment of hypothyroidism and the use of TH in euthyroid individuals. The questionnaire was translated from English into German by a bilingual physician and checked by a senior bilingual physician. An open-access survey platform (link to the German version of SurveyMonkey: https://de.surveymonkey.com/r/QZBDFLP) was used to build and distribute the questionnaire, and a written introduction preceded the survey. Eight questions about demographic data (section A) were followed by twenty-three questions about the use of thyroid hormones for hypothyroid and euthyroid patients (section B) (**supplementary material 1**).

An e-mail with an electronic link leading to the voluntary and anonymized questionnaire was sent to all members of the Thyroid Section of the German Endocrine Society (DGE) on 26th January 2021, followed by three reminders between February and March 2021. Data were accessible to the authors only by password. Repeat submissions from the same IP-address were automatically blocked; confidentiality was preserved, and the study observed the

rules on personal data protection. Ethical approval was not necessary in view of the nature of the survey. The thyroid section of the DGE is a thyroid expert group and comprises endocrinologists, nuclear medicine specialists, endocrine surgeons, pathologists, pediatricians, and basic researchers.

Statistical Analysis

Descriptive statistics were prepared for responses to all questions. Respondents with incomplete demographic data were excluded. In all analyses, respondents who did not know the answer to a question were pooled with respondents who did not provide an answer. As not every respondent answered every question, the percentage of respondents providing a given answer was calculated individually for each question, using the number of respondents to that question as the denominator. Pearson's x^2-test was used to compare frequencies between the categorical variables. Multiple logistic regression analysis was performed to examine various predictor variables. A two-sided p-value of < 0.05 was considered statistically significant. All analyses were conducted using IBM SPSS statistics software version 27 (SPSS Inc., Chicago, IL, USA). GraphPad Prism, version 5.02 (GraphPad Software Inc, La Jolla, CA, USA), was used to prepare figures.

Results

Sample characteristics

Out of 206 members of the Thyroid Section of the German Endocrine Society (DGE), 163 (79.1 %, 163/206) completed the survey, and their answers were included in the study. The demographic data of the respondents are shown in ▶ **Table 1**. Demographics (questions "gender," "years in medical practice," "accredited specialty") were answered by all respondents. Besides being members of DGE, nine respondents (4.9 %) were members of the American Thyroid Association (ATA), and 16 (8.7 %) were members of the European Thyroid Association (ETA).

A total of 125 members (76.7 %, 125/163) responded that they see thyroid patients daily, while 35 (21.5 %, 35/163) reported weekly attendance to thyroid clinics. Of all responders, 119 (73 %, 119/163) members treated > 100 hypothyroid patients annually, 27 (16.6 %, 27/163) managed 51–100 per year, 16 (9.8 %, 16/163) cared for 10–50 annually.

Treating hypothyroid patients

One hundred and thirty-eight (98.6 % 138/140) stated that they use LT4 as the first-line treatment for patients with hypothyroidism. Twenty-three individuals did not provide an answer to their first treatment of choice, but none of the members suggested DTE as the initial substitution therapy. One respondent (0.7 %, 1/140) suggested monotherapy with LT3 or LT4 + LT3, as first choice for treatment of hypothyroid patients (LT4 vs. LT3, $p < 0.001$; LT4 vs. LT4 + LT3, $P < 0.001$).

Although combination therapy was not their first-line therapy, 45.4 % (74/163) of the respondents also prescribed LT4 + LT3, 4.9 % (8/163) DTE, and 23.3 % (38/163) LT3 for selected conditions in their daily clinical practice.

▶ **Table 1** Characteristics of respondents ($n = 163$)

		n (%)
Gender		
	Female	81 (49.7)
	Male	82 (50.3)
Age in years		
	20–30	5 (3.1)
	31–40	15 (9.2)
	41–50	52 (31.9)
	51–60	58 (35.6)
	61–70	21 (12.9)
	70 +	12 (7.4)
Years in medical practice		
	0–10	22 (13.5)
	11–20	50 (30.7)
	21–30	51 (31.3)
	31–40	27 (16.6)
	40 +	13 (8.0)
Accredited Specialty*		
	Endocrinology#	138 (84.7)
	Internal medicine	88 (54.0)
	Pediatric endocrinology	7 (4.7)
	Nuclear medicine	10 (6.1)
	Surgery	3 (1.8)
	Family Medicine	1 (0.6)
	Gynecology	1 (0.6)
	Others**	7 (4.3)
Place of employment*		
	University centre	44 (24.2)
	Regional hospital	24 (13.2)
	Private clinic	10 (5.5)
	General practice	8 (4.4)
	Basic researcher	1 (0.5)
	Specialist practice („Facharztpraxis")	95 (52.2)
Member of*		
	European Thyroid Association (ETA)	16 (8.7)
	American Thyroid Association (ATA)	9 (4.9)
	German Endocrine Society (DGE)	149 (81.0)
	Others	10 (5.4)
Activity		
	Clinical active	151 (92.6)

*The sum of *n* exceeds n = 163 because multiple options may have been selected; percentage is given for respondents. **other specialties (diabetology ($n = 4$), nephrology (n = 1), gastroenterology ($n = 1$), andrology ($n = 1$)). # Some of the respondents ($n = 82$) selected endocrinology as well as internal medicine as specialization.

Using different LT4 formulations

Most of the respondents (80 %, 112/140) indicated that they decided the dispensed LT4 formulation, while only 10.7 % (15/140) indicated that they have no influence on this matter. Only 12 respondents (8.6 %, 12/140) answered that the type of dispensed LT4

was mostly chosen by general practitioners (LT4 dispensed as prescribed vs. chosen by general practitioners; p < 0.001).

In the survey, five questions explored the use of different LT4 formulations in specific situations (▶ **Table 2**). Most German thyroidologists preferred LT4 tablets to soft-gel capsules or liquid LT4 for the treatment of hypothyroidism, and they did not expect any significant difference when switching from one formulation to another. The same attitude applied to situations with interfering drugs, intolerance to various foods, unexplained poor biochemical control, or persistent symptoms despite reasonable biochemical control. Only a minority of responding thyroid specialists use the new LT4 formulations in situations with an expected lower absorption and reduced bioavailability of LT4 tablets (prescribing tablets vs. "I expect no major changes with the different formulations"; p < 0.001, tablets vs. soft-gel capsules; p = 0.48, tablets vs. liquid solution; p < 0.001).

In a logistic regression analysis (▶ **Table 3**), 3.2 times more female than male responders would switch to tablets from another manufacturer when faced with biochemically euthyroid but symptomatic patients, the other choices being "soft-gel capsules," "liquid LT4 solution," or "no major changes expected with different formulations" (Question #B9: (p = 0.021). Furthermore, female responders relate significantly to switching LT4 tablets from another manufacturer (p = 0.014). To the question covering poor biochemical control of hypothyroidism, respondents without membership of either ETA or ATA were not as likely (question #B7 in ▶ **Table 2**) and question #B8 in ▶ **Table 2**) to stick to "tablets," as compared to colleagues with a membership of one of these associations.

Monitoring thyroid hormone treatment

After initiating LT4 treatment (61.4 % (86/140) members of the Thyroid Section of the DGE would re-check serum TSH concentrations after 4–6 weeks, and 37.9 % (53/140) after eight weeks. No member would re-check after only two weeks, and 23 of the members did not provide a definite answer (4–6 weeks vs. 8 weeks; p < 0.001).

Most respondents would re-check serum TSH after 4–6 weeks (49.3 %, 69/140) when switching to another formulation or changing to another manufacturer, and 42.1 % (59/140) would re-check after 8 weeks. If the dosage was unchanged, six members (4.3 %, 6/140) stated that there is no need for TSH monitoring when switching from one preparation to another, six members (4.3 %, 6/140) relied on clinical evaluation, and 23 members did not answer (4–6 weeks vs. 8 weeks; p < 0.001). The answers were not associated with any of the investigated demographic variables of the respondents, such as gender, age, years in medical practice, member of ETA/ETA, or the number of patients treated annually.

Treating euthyroid patients with thyroid hormones

This section explored physicians' attitudes towards prescribing TH to euthyroid patients in specific clinical situations. A minority of the respondents (26.4 %, 37/140) stated that TH treatment in euthyroid patients is never indicated (never indicated vs. others; p < 0.001; never indicated vs. "in patients with unexplained fatigue"; p = 0.015, never indicated vs. "in patients with severe hypercholesterolemia, as a complementary treatment"; p = 0.007, never indicated vs. "in patients with simple goiter"; p < 0.001, never indicated vs. "in patients with obesity resistant to lifestyle interventions"; p = 0.143, never indicated vs. "in patients with depression resistant to anti-depressant medications," p = 0.09). The ma-

▶ **Table 2** Levothyroxine formulations preferred by the members of the Thyroid Section of German Endocrine Society (DGE) in different clinical situations

	I expect no major changes with different formulations, *n (%)*	**Tablets/tablets from another manufacturer, *n (%)***	**Soft-gel capsules, *n (%)***	**Liquid solutions, *n (%)***	**Not sure/ no answer, *n (%)***
B5. Interfering drugs may influence the stability of therapy. Which LT4 preparations, in your experience, are least likely to be subject to variable absorption?	55 (33.7)	54 (33.1)	1 (0.6)	30 (18.4)	23 (14.2)
B6. Which of the following preparations of LT4 would you prescribe in case of the first diagnosis of hypothyroidism when the patient self-reports intolerance to various foods raising the possibility of celiac disease, malabsorption, lactose intolerance, or intolerance to common excipients?	31 (19.0)	67 (41.1)	3 (1.8)	39 (23.9)	23 (14.2)
B7. Which of the following preparations of LT4 would you prescribe for a patient established on LT4 who has unexplained poor biochemical control of hypothyroidism?	37 (22.7)	61 (37.4)	4 (2.5)	38 (23.3)	23 (14.2)
B8. Which of the following preparations of LT4 would you prescribe for a patient with poor biochemical control who is unable (due to a busy lifestyle) to take LT4 fasted and separate from food/drink?	52 (31.9)	41 (25.2)	5 (3.1)	42 (25.8)	23 (14.2)
B9. Which of the following preparations of LT4 would you prescribe for a patient established on LT4 tablets who have good biochemical control of hypothyroidism but continues to have symptoms?	106 (65)	25 (15.3)	0 (0)	5 (31.0)	27 (16.6)

B# refers to the number of the question in the THESIS questionnaire, *LT*4 levothyroxine, *n* numbers

▶ **Table 3** Multivariate logistic regression analysis concerning question number ▶ **B9** in the THESIS questionnaire (Clinical scenario 4: Patient established on LT4 who has good biochemical control of hypothyroidism but continues to have symptoms) for the dependent variable "▶ **Tablets from another manufacturer** " and various independent variables. LT4, levothyroxine

	Regression coefficient B	*P*	Exp (B) (OR)	CI 95 %
Gender (female)	1.185	**0.021**	**3.271**	1.2 – 8.918
Age (reference category: 20–30 years)		0.505		
Age (31–40 years)	− 1.455	0.256	0.233	0.019 – 2.877
Age (41–50 years)	− 0.701	0.581	0.496	0.041 – 5.979
Age (51–60 years)	− 0.018	0.989	0.982	0.067 – 14.396
Age (61–70 years)	0.898	0.563	2.454	0.117 – 51.552
Age (> 70 years)	− 18.046	0.999	0	
Years in medical practice (reference category: 0–10 years)		0,726		
Years in medical practice (11–20 years)	− 1.08	0.204	0.34	0.064 – 1.798
Years in medical practice (21–30 years)	− 0.531	0.564	0.588	0.097 – 3.567
Years in medical practice (31–40 years)	− 0.948	0.411	0.387	0.04 – 3.723
Years in medical practice (> 40 years)	− 20.39	0.998	0	
Member of (member of ETA or ATA)	− 1.129	0.09	0.323	0.088 – 1.194
Number of patients with hypothyroidism treated (reference category: 10–50/year)		0.833		
Number of patients with hypothyroidism treated (51–100/year)	− 0.546	0.536	0.579	0.103 – 3.263
Number of patients with hypothyroidism treated (> 100/year)	− 0.724	0.353	0.485	0.105 – 2.238
Number of patients with hypothyroidism treated (no, rarely)	17.911	1	60091581.9	

OR, odds ratio <; CI, confidence interval; ATA, American Thyroid Association; ETA, European Thyroid Association

jority (62.9 %, 88/140) indicated that TH treatment could be considered in infertile females with high levels of thyroid antibodies (indicated in female infertility vs. no indication; $p < 0.001$), and a large number (57.1 %, 80/140) would also consider TH therapy in patients with simple goiter growing over time. Only a small number of respondents would consider TH prescription in patients with treatment-resistant depression (6.4 %, 9/140), unexplained fatigue (12.9 %, 18/140), obesity resistant to lifestyle interventions (5.0 %, 7/140), or severe hypercholesterolemia as a complementary treatment (7.1 %, 10/140) (▶ **Fig. 1**).

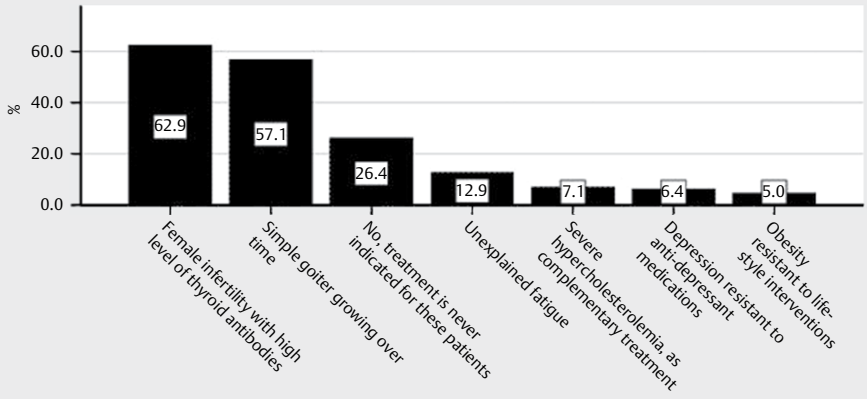
In a logistic regression analysis (**Supplementary Table 1**), 10.2 times more responders with an experience of 21–50 years versus 0–10 years in medical practice would consider TH therapy in female infertility with high levels of thyroid antibodies (question #B1: "Thyroid hormones may be indicated in biochemically euthyroid patients with:"). For the other options ("unexplained fatigue", "severe hypercholesterolemia, as a complementary treatment," "depression resistant to antidepressant medications," "simple goiter growing over time" and "no, treatment is never indicated for these patients," respectively) to this question, demographic variables had no impact on the stated answers.

Combination therapy with LT4 and LT3

A majority of respondents (94; 67.1 %, 94/140) considered as appropriate the switch from LT-4 to combination therapy for patients with normal serum TSH and persistent symptoms suggestive of hypothyroidism. Only 24.3 % (34/140) of respondents would never use combination therapy due to the low quality of evidence. No less than 5.7 % (8/140) would recommend LT4-LT3 treatment also to patients with normal serum TSH and unexplained weight gain. Four (2.9 %, 4/140) respondents considered the use of combination therapy in patients recovering from protracted hypothyroidism, and twenty-three members did not provide an answer to this question (combination therapy vs. "never use"; $p < 0.001$). Thyroid specialists aged 51–60 years old considered combination therapy in patients with normal serum TSH who still complain of symptoms suggestive of hypothyroidism 12 times more often than younger members (20–30 years) (**supplementary Table 2**). Other than age, demographic variables had no impact on the stated answers based on multivariate analysis.

Persistent symptoms in LT4 treated patients

Twenty-nine respondents (20.7 %, 29/140) estimated that up to 30 % of hypothyroid patients still experience persistent symptoms despite the attainment of biochemical euthyroidism while on LT4 therapy, and 10 (7.1 %, 10/140) claimed that > 30 % of the patients have persistent symptoms despite normal TSH levels. The majority of the respondents, however, estimated this fraction of patients to be as low as 6–10 % (30.1 %, 49/140) or less than 5 % (28.2 %, 46/140); (≤ 10 % vs. > 10 %, $p < 0.001$). Forty-eight thyroid specialists (34.3 %, 48/140) answered that this trend has increased over the past five years, 70 (50.0 %, 70/140) did not observe a significant change, ten (7.1 %, 10/140) declared that these cases are decreasing, twelve members (8.6 %, 12/140) were not sure, and the rest of them (23/163) did not provide an answer (more cases vs. fewer cases; $p = 0.041$). Responders treating 51–100 patients with hypothyroidism/year were 4.4 times more certain that patient benefit from TH therapy had "not changed" than members treating only 10–50 hypothyroid patients/year (**Supplementary Table 3**). The



▶ **Fig. 1** Responses from 140 German thyroidologists concerning the use of thyroid hormones in euthyroid individuals (Question B1: "Thyroid hormones may be indicated in biochemically euthyroid patients with: *[check all that apply]*". Twenty-three respondents did not answer this question. Total frequency was > 100 % as more than one option was possible in the questionnaire.

outcome of the rest of these questions did not depend on any of the demographic variables stated above.

Regarding possible reasons for persistent hypothyroid symptoms, German thyroid specialists were asked to comment on eight possible causes with five options (strongly disagree, disagree, neutral, agree, strongly agree). While most respondents selected the "neutral" option neutral, some responders suggested that persistent symptoms could be due to psychological factors, comorbidities, unrealistic expectations, chronic fatigue syndrome, inflammation or autoimmunity, the burden of chronic disease, or the burden of taking medication (▶ **Fig. 2**). Only a minority stated that symptom persistence might be due to LT4's inability to restore normal TH physiology (▶ **Fig. 2**). Members of ETA or ATA strongly agreed with the statement that "in most patients treated with levothyroxine who achieved normal serum TSH, persistent symptoms are due to the inability of levothyroxine to restore normal physiology" (Question #B16 in the questionnaire) 14.4 times more than non-ETA or ATA members; no association, particularly with the age of responders, was observed (Supplementary Table 4).

Supplementation with selenium or iodine

Fifty-nine (42.1 %, 59/140) experts answered that supplementation with selenium or iodine could be used if requested by the patient ($p < 0.001$), while 22 (15.7 %, 22/140) stated that such supplementation should never be used ($p < 0.001$). A total of 52 respondents (37.1 %, 52/140) answered that selenium or iodine may be used in patients with co-existing autoimmune thyroiditis ($p < 0.001$). Only seven respondents (5.0 %, 7/140) recommended supplementation with selenium or iodine to patients with subclinical hypothyroidism ($p = 0.241$), while twenty-three did not provide an answer. The outcome in questions regarding supplementations does depend on some demographic variables. Thus, supplementation with selenium or iodine at the patient's request or as a complementary treatment was preferred 8.1 times more by non-members of ETA or ATA than ETA/ATA members ($p = 0.010$) (**supplementary Table 5**). Supplementation with selenium or iodine in coexisting autoimmune thyroiditis was preferred 3.2 times more by members of ETA or ATA than non-ETA or ATA members ($p = 0.032$) (**supplementary Table 6**). Regarding supplementation with selenium or iodine in subclinical hypothyroidism, demographic variables had no impact on the stated answers on the basis of multivariate analysis.

Endocrinologists with hypothyroidism

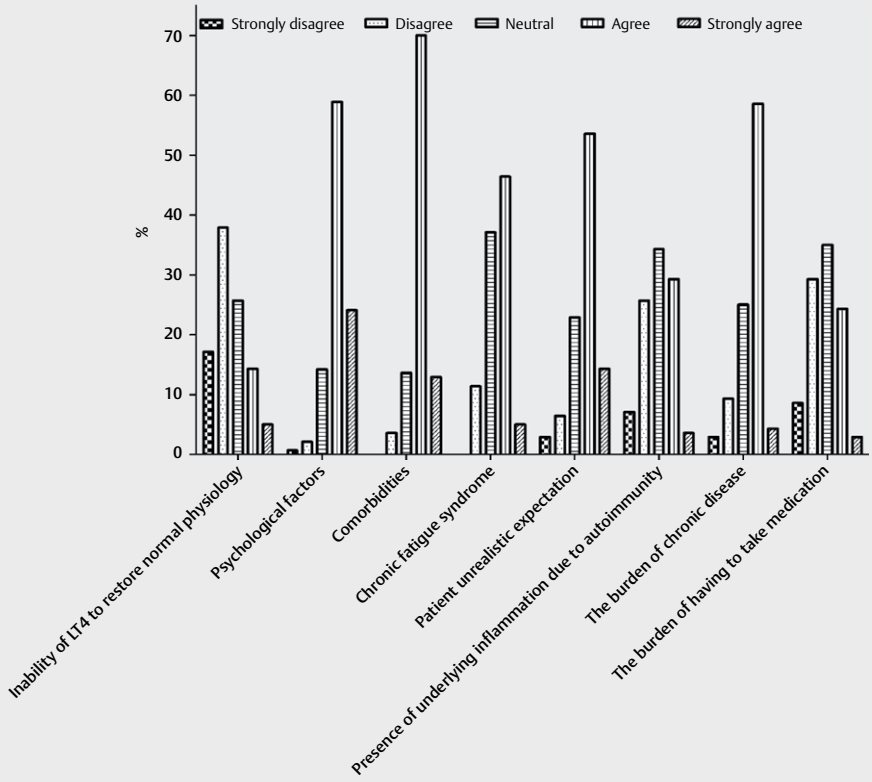
Twenty respondents (14.3 %, 20/140) reported their own medical history of hypothyroidism requiring treatment, 120 respondents (85.7 %, 120/140) had no history of hypothyroidism ($p < 0.001$), 23 respondents did not respond. Only four (22.2 %, 4/18) respondents declared suffering from excessive tiredness, whereas two (of 20 respondents with their medical history of hypothyroidism) did not respond to this question. To the question #B20 ("Have you tried combination treatment with LT4 or LT3?") as well as the question #B21 ("Do you have tried thyroid treatment with DTE?", two (of 20 respondents with their medical history of hypothyroidism) did not respond, six (33.3 %, 6/18) respondents tried, 12 (66.7 %, 12/18) did not try combination therapy. Two (11.1 %, 2/18) respondents tried treatment with DTE and 16 (88.9 %, 16/18) did not try treatment with DTE (tried vs. not tried, $p < 0.001$).

One-hundred-and-two respondents (75 %, 102/136) would not consider combination therapy with LT4 and LT3 or with DTE, and 34 (25 %, 34/136) might consider combination therapy in case they were to be affected by hypothyroidism in the future (would consider vs. would not consider combination therapy, $p < 0.001$).

Discussion

Treatment with LT4

This survey among members of the Thyroid Section of the DGE confirmed that LT4 is the treatment of choice for newly diagnosed hypothyroid patients in Germany [27]. LT4 tablets, liquid solution, and soft-gel preparations are commercially available in Germany. However, only 3.6 % (5/140) of respondents would consider prescribing soft-gel capsules and 30 % (42/140) liquid solution, respectively, to patients for whom it is inconvenient to separate LT4 and



▶ **Fig. 2** The opinion of German thyroidologists on possible factors explaining persistent symptoms of hypothyroidism despite biochemical euthyroidism in patients treated with LT4.

food intake. The reason for this attitude is unknown, but probably cost-effectiveness and user aspects may be issues [2]. LT4 soft-gel capsules (Tirosint® 100 µg) contain animal gelatin, which some patients may wish to avoid for personal reasons. In Germany, LT4 soft-gel capsules (Tirosint® 100 µg) are three times more expensive than LT4 tablets (e. g., L-Thyrox Hexal® 100 µg). LT4 as a liquid solution (in Germany, L-Thyroxine Henning Tropfen 30 mL, 100 µg/mL) is less convenient to use (drop counting) and to store (cold storage). This is in line with the reports of the French [28], Bulgarian [29], Finnish [30], Swedish [31], and Polish [32] surveys, where the majority of the respondents would also prefer LT4 tablets.

In contrast, 75 % of respondents in the Italian survey [11] and 74 % in the Romanian survey [33] recommended soft-gel capsules or liquid solutions to patients on LT4 therapy who have poor biochemical control of their hypothyroidism. Interestingly, only 14.5 % of the Danish endocrinologists [34] and only 30 % (2.9 % soft-gel, 27.1 % liquid solution) of the German thyroidologists agreed with this strategy. Soft-gel capsules have been on the Italian market for a longer time than in Germany. Thus, Italian endocrinologists are probably more familiar with other formulations of LT4 than tablets. Other factors explaining why soft-capsules are more frequently prescribed in Italy than in other countries could be differences in cost and marketing and the fact that most studies on efficacy, safety, and bioavailability of soft-gel capsules have so far been conducted in Italy.

Thyroid hormone therapy in euthyroid patients

In accordance with current guidelines [13, 35], most responders in the German survey agreed that TH therapy is not indicated in treatment-naïve euthyroid patients. About 63 % (88/140) of German thyroidologists, however, would consider thyroid hormone supplementation for infertile women with high levels of thyroid autoantibodies. This is in agreement with reports from the Polish (63.4 %) survey [32] but significantly higher than in other countries in the THESIS survey, namely 48.5 % of the Spanish [36], 36.4 % of the Romanian [33], 47.3 % of the Swedish [31], 42.1 % of the Danish [34], 31.7 % of the French [37], 30 % of the Finnish survey, and 17.5 % of the Bulgarian [29] survey. These data were at least partially in agreement with the 2012 ETA guidelines [13], stating that treatment with LT4 might be considered in some euthyroid thyroid peroxidase antibody (TPOAb)-positive women undergoing fertility treatment, in whom plasma TSH is within the upper normal reference range (i. e., 2.5–4.0 mIU/L). The rationale being to secure euthyroidism in case of pregnancy, although LT4 treatment neither promotes conception nor reduces the risk of pregnancy complications in such individuals [38, 39]. Notably, the most recent 2021 ETA guideline recommends that all women with subfertility should be screened for TPOAb and suggests that in subfertile women, LT4 treatment should be started promptly in case of overt hypothyroidism or when TSH levels are above 4.0 mIU/L or the upper limit of reference range [40].

Interestingly 57.1 % (80/140) of responders in the German survey agreed to treat euthyroid patients with a growing goiter with LT4. Our results are in line with reports from the Bulgarian (35 %) [29], the Romanian (39.4 %) [33], the French (40.2 %) [37], the Polish 40.3 %) [32], and the Finnish (41 %) surveys, but a lot higher than in the Danish (12.5 %) [34], the Swedish 15.1 % [31], the Italian (18.1 %) [11], and the Spanish (21.1 %) [36] surveys. However, the current guidelines discourage this approach, and action is needed to attain a more appropriate management of these euthyroid patients, especially in iodine-sufficient regions of Europe [41].

Combination therapy with LT4 and LT3 and supplementation with selenium or iodine

According to ETA guidelines [13], the LT4 + LT3 combination may be used as an alternative to LT4 in patients with persistent symptoms of hypothyroidism despite stable biochemical control for at least six months, and after the exclusion of interfering conditions. If improvement is not achieved after 3–6 months, the combination therapy should be discontinued. This consideration was supported by 67.1 % (94/140) of the German thyroid specialists, and 52.9 % (74/140) reported to have prescribed combination therapy in clinical practice. This is in agreement with reports from other countries in the THESIS survey, where 78.5 % of Swedish [31] and 71 % of the Danish [34] respondents would prescribe LT4 + LT3 combination therapy in the presence of persistent symptoms suggestive of hypothyroidism, but a lot higher than in the Finnish (43 %), Italian (40 %) [11], Spanish (40 %) [36], Romanian (35.9 %) [33], Polish (32.2 %) [32], French (26.0 %) [37], and Bulgarian (24.2 %) [29] surveys.

In the German survey, older physicians (51–60 years old) were 12 times more likely to prescribe LT4 + LT3, but they did not believe more than younger physicians that "in most patients treated with LT4 who achieved normal serum TSH, persistent symptoms are due to inability of LT4 to restore normal physiology". This apparent discrepancy may be consequent upon patients exerting pressure on thyroid specialists to prescribe combination treatment [42].

Finally, only very few German thyroid specialists considered the use of DTE, which is characterized by a high content of T3 and has not been shown to result in better outcomes compared to synthetic LT4 in a randomized controlled trial [43].

Of note, almost one-third of German thyroid specialists would consider selenium or iodine supplementation in patients with autoimmune thyroiditis, which, however, is not recommended to patients with autoimmune thyroiditis according to a recent ETA survey on the use of selenium supplementation in Hashimoto's thyroiditis, showing poor evidence for clinical efficacy of selenium supplementation [44], although an effect on TPO antibody levels was shown in a meta-analysis [45]. The results in the German survey are in agreement with reports from other countries in the THESIS survey, where 29.6 % of the Polish [32], 30 % of the Finnish [30], and 56.8 % of the Romanian [33] respondents would prescribe selenium or iodine supplementation, but a lot higher than in the Danish (6.6 %) [34], Swedish (4.3 %) [31], French (10.1 %) [37], Spanish (14.1 %), and Bulgarian (15 %) [29] surveys.

Treatment of physicians with hypothyroidism

Most respondents declared that they would not consider TH combination therapy for their treatment if they were to develop hypothyroidism, primarily based on a lack of evidence. Those considering combination therapy would prefer LT4 + LT3, while DTE was rejected due to the non-physiologically high T3:T4-ratio. Interestingly, 45.4 % of the respondents would prescribe combination therapy for their patients with hypothyroidism, but only 25 % would consider this treatment for themselves if they developed hypothyroidism. This is in agreement with reports from other THESIS surveys, where 21.7 % of the Swedish [31] and 18. % of the Danish [34] respondents would consider a combination therapy with LT4 + LT3 or DTE for themselves if they developed hypothyroidism, but the values were a lot higher than in the French (9.3 %) [28], Polish (11.8 %) [32], Bulgarian (15 %) [29], and Spanish (17.3 %) [36] surveys. The discrepancy in predisposition to use LT4 + LT3 combination therapy for patients compared to oneself among thyroid specialists suggests that factors other than evidence influence clinical decisions, most likely related to the ambiguity of professional guidelines and demands made by patients.

Strengths and limitations

The strength of this survey is the relatively high response rate, as compared to similar THESIS surveys [11, 28, 30–34, 36], with a response rate of 26.2 % by the Spanish [36], 28.1 % by the French [28], 28.2 % by the Swedish [31], 30.0 % by the Finnish [30], 31.2 % by the Danish [34], 42.2 % by the Romanian [33], 43.5 % by the Italian [11], and 59.5 % by the Polish [32] survey. By circulating the questionnaire to all 206 members of the Thyroid Section of the DGE, we obtained 163 responses (79.1 % response rate), and more than 90 % of thyroid specialists reported seeing hypothyroid patients daily or at least weekly. Most DGE members who are clinically and academically active within the thyroid field are organized within the Thyroid Section of the DGE. In nearly all other THESIS surveys [11, 28, 30–34, 36], the questionnaire was distributed to all members of an Endocrine Society; limitations also include the virtual patient cases with loss of nuances potentially interfering with the interpretation. Another limitation is that treatment of hypothyroidism, particularly LT4 prescription, in Germany is initiated mostly by family doctors/general practitioners, who were not represented in this survey.

In conclusion, in Germany, the treatment of choice for hypothyroidism is LT4 tablets, also when conditions possibly affecting LT4 bioavailability are present. Combination therapy with LT4 + LT3 is considered for patients treated with LT4 with persistent symptoms and stable TSH within the reference range, while only very few members of the Thyroid Section of the DGE prescribe DTE. Notably, the outcome in questions regarding "the LT4 + LT3 combination therapy", "estimates on hypothyroid patients experience persistent symptoms despite biochemical euthyroidism while on LT4 therapy", and "supplementation with selenium and iodine" depend on the demographic variables of the respondents.

L-T4 treatment of infertile euthyroid women harboring thyroid antibodies, which is not evidence-based, is considered by about 63 % of German thyroid specialists. German thyroid specialists differ from other national survey respondents in their selenium and iodine supplementation recommendations, which warrants further study.

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Conflict of Interest

LH, RA, EVN, EP, and PP have received consultancy fees from IBSA Institute Biochimique SA. The remaining authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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