Real-life practice of thyroid hormone use in hypothyroid and euthyroid patients: a detailed view from the THESIS questionnaire survey in France

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*THESIS: **T**reatment of **H**ypothyroidism in **E**urope by **S**pecialists: an **I**nternational **S**urvey

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Abstract

Aim: To describe practices of French physicians regarding thyroid hormone therapy focusing on available LT4 formulations.

Material and Methods: Members of the French Endocrine Society (FES) and affiliated Societies (Endocrine Tumor Group Societies, The French College of Teachers of Endocrinology, Diabetes and Metabolic Diseases and the Union of Endocrinologists, Diabetologists, Nutritionists and Metabolic diseases) were invited to participate in an online survey.

Results: Out of 2094 invitations, 535 (25.5 %) completed the survey and were included in the analysis. The vast majority (99.4%) reported that levothyroxine (LT4) is the treatment of choice for hypothyroidism. Liothyronine (LT3) or a combination of LT4 and LT3 were considered by 7.1% and 14.2% of responders respectively, for the treatment of hypothyroidism, mainly when symptoms persisted despite achieving normal TSH concentration on LT4 therapy. Forty-four percent of responders stated that thyroid hormone treatment is never indicated in euthyroid patients, while the remainder would consider treating euthyroid patients with a goiter growing over time (40.2%) and/or euthyroid women with positive anti-TPO antibodies and infertility (31.7%). LT4 tablets were the preferred LT4 formulation. A significant proportion of FES members expected no major clinical differences upon changing to formulations such as soft-gel capsules and liquid solutions, even in specific scenarios such as poor biochemical control or suspicion of malabsorption.

Conclusion: The treatment of choice for hypothyroidism in France is LT4. LT3-based therapy is considered by some physicians in case of persistent symptoms of hypothyroidism despite normal TSH level. A significant proportion of responders (66.0%) stated that they would consider treating euthyroid patients, contrary to current evidence. These outdated practices should be addressed by professional bodies such as the FES.

Introduction

Hypothyroidism is a common disease with an annual incidence in France of 3.1/1000 in women and 0.2/1000 in men (1). The National Health Data System indicates that a total of 3 million patients use a levothyroxine (LT4)-based product in France, predominantly women (86%) corresponding to about 4.5% of the total French population (2). Data from the National Health Data System also demonstrated an increase in the sales of LT4-based drugs between 1990 and 2012 leveling off after 2012 (2).

Since 2017 there has been a progressive increase in the availability of LT4-based products in France with the development of different tablet formulations and soft-gel capsules in addition to the pre-existing liquid solutions available since the 80's. It has been suggested that such formulations overcome the reduced bioavailability noted with LT4 tablets, when administrered simultaneously with food or beverages or other types of medications (proton-pump inhibitors, calcium or iron supplements) (3). However, the prescription of these more expensive LT4-based preparations, such as soft-gel capsule formulations, creates a financial burden in view of the relatively high prevalence of hypothyroidism in France, and the absence of indisputable evidence of cost-effectiveness (4).

Poor quality of life (QoL) in patients treated with thyroid hormones has been highlighted (5 , 6, 7). Randomised controlled trials have not demonstrated improvement in QoL in patients treated with combination of LT4+LT3 (5) and therefore many other parameters (behavioral, cognitive and/or lifestyle factors) may be relevant (5, 8).

French national recommendations for the management of hypothyroidism are available. One, regarding the management of thyroid dysfunction in the elderly, was published under the aegis of the French Endocrine Society (FES) in 2019 (9) and the others were issued by the French National Authority for Health in 2019 and 2007

(https://www.has sante.fr/jcms/c_2910740/fr/pertinence-des-soins-hypothyroidie; https://www.has-sante.fr/jcms/c_598104/fr/hypothyroidies-frustes-chez-l-adulte-diagnostic-et-prise-en-charge). Key recommendations were: (a) no TSH screening of the general asymptomatic adult population; (b) asymptomatic patients with subclinical hypothyroidism and a serum TSH less than 10 mIU/L need not be treated; (c) serum TSH measurements should be repeated at 6–8 weeks after initiating treatment or after a change in dose or brand or formulation. Those last 2 recommendations were mainly intended for general practitioners who mostly diagnose and treat hypothyroid patients, although endocrinologists, mainly in private practice, also routinely follow hypothyroid patients.

This French survey was part of an ongoing international project referred to as THESIS (*T*reatment of *H*ypothyroidism in *E*urope by *S*pecialists: An *I*nternational *S*urvey). France was among 28 participating countries across Europe invited to take part in this project. The aim was to identify current attitudes of French physicians, related to thyroid hormone treatment, in a European country where all LT4 formulations, as well as LT4+LT3 combination, are available on the market.

Methods

Survey

A questionnaire was developed to evaluate the opinion of European endocrinologists on the treatment with thyroid hormones. The original survey in English (supplementary material 1) was translated into French by a bilingual clinician, and subsequently checked by a bilingual senior clinician.

The SurveyMonkey platform was used. Attempted repeat submissions from the same IP address were automatically blocked. E-mails from the President of the FES, including an electronic link to the questionnaire, followed by 5 reminders were sent

to all members of the FES (n = 1611) and related Societies (Endocrine Tumor Group Societies, The French College of Teachers of Endocrinology, Diabetes and Metabolic Diseases and the Union of Endocrinologists, Diabetologists, Nutritionists and Metabolic diseases; n = 2094 in total) from January 11th to April 5th, 2021. Completion of the survey took approximately 10 minutes. Eight questions about demographic data were followed by 23 questions about the management of hypothyroidism. A total of 535 responses were included in the analysis among 1935 endocrinologist practicing in France (data from the French National Medical Council), of whom 492 completed all questions of the survey.

Statistical analysis

Qualitative variables were reported using frequencies and quantitative variables using mean and standard deviation. Chi-square tests were used when testing the association between qualitative variables. Univariate and multivariate logistic regression were applied to assess the association between each endpoint and demographic characteristics (age, sex, place of employment, membership of ETA/ATA or number of patients treated annually). Multivariate logistic regressions were established using a backward selection of factors based on likelihood ratio testing. Level of statistical significance was fixed at 5%. For analyzing the place of employment, responders being exclusively in public service (University Center, Regional Hospital and Research) were grouped and compared with the other responders.

Only data from responders who had completed all questions about demographic data were considered eligible for statistical analysis (Supplementary Material 2).

Despite the number of endpoints, no multiple testing correction was done as the aim of this study was exploratory. Analyses were performed using R version 3.5.1.

Results

Sample characteristics

A total of 588/2094 (28.1%) members responded of whom 53/2094 (2.5%) were excluded because of incomplete demographic data. Table 1 summarizes the characteristics of the 535 responders included in the analyses. Besides being members of the French Endocrine Society, 38 (7.1%) were also members of the European Thyroid Association and 5 (0.9%) of the American Thyroid Association.

[b] Responders who did not answer "private clinic" or "general practice" or "private practice" were considered as having exclusive public practice (University Center and/or Regional Hospital and/or Research).

Most responders treated patients with thyroid diseases frequently, 351/535 (65.6%) daily and 165/535 (30.8%) weekly. Only 19/535 (3.6%) treated hypothyroid patients rarely. More than 100 hypothyroid patients/year were treated by 305/533 (57.2%) responders, 51-100 annually by 149/533 (28.0%), 10-50 by 75/533 (14.1%) and fewer patients by only 6/533 (0.7%) responders.

Treating hypothyroid patients

Virtually all responders (489/492, 99.4%) used LT4 as the treatment of choice for hypothyroid patients. Only 3 responders favored LT4+LT3 combination therapy (n = 2) or LT3 monotherapy (n = 1) as treatment of choice and 43 did not provide an answer (LT4 *vs* other thyroid hormone regimens; P <0.0001). Although LT3-based therapy is not a treatment of choice for most of the FES members, 76/535 (14.2%)

indicated that they prescribe LT4+LT3 combination therapy and 38/535 (7.1%) LT3 alone, in certain circumstances. Only one respondent would prescribe desiccated thyroid extract, which is not available in France. For responders who could consider at least one alternative to LT4 alone (LT4+LT3 combination or LT3 alone, or desiccated thyroid extract), 68/91 (75%) were in private practice (P <0.0001). In the multivariate analysis, both place of employment (ODDS Ratio – OR: 0.2 [0.1-0.4]; *P* <0.0001), public service and the number of years of medical practice (OR: 2.2 [1.2-4.3] for 21-30 years; OR: 2.2 [1.1-4.3] for 11-20 years; *P* = 0.02) remained significant (supplementary Material 3).

Most of the responders (N = 466/535; 87.1%) indicated that their patients were dispensed the LT4 formulation that had been prescribed, including 28/535 (5.2%) who had to provide justification to the regulatory authorities to ensure that the prescribed formulation was dispensed. Three responders/535 (0.6%) answered that mostly general practitioners decide on the type of LT4 dispensed, and 23/535 (4.3%) had no control on this matter.

Using different LT4 formulations

In France, the treatment of choice for hypothyroidism is LT4. In specific situations detailed in Table 2, members of the FES considered the use of some formulations of LT4 in preference to others (among soft-gel capsules, liquid solution, tablets).

On the whole, most French physicians preferred LT4 tablets to soft-gel capsules or liquid solution, and did not expect major changes when switching from one formulation to another, in many different situations such as taking potentially interfering drugs, gastro-intestinal comorbidities (intolerance to various foods raising the possibility of celiac disease, malabsorption, lactose intolerance or intolerance to excipients) or unexplained poor biochemical control of hypothyroidism. In a univariate logistic regression analysis, it was demonstrated that male physicians were more likely to indicate “tablets” or “no major changes” than

other physicians regarding the question "Which of the following preparations of LT4 would you prescribe for a patient established on LT4 who has unexplained poor biochemical control of hypothyroidism?" (OR: 1.89; 95% confidence interval (95% CI): [1.2-3]; *P* = 0.006), while physicians having less than 20 years of medical practice were less likely to indicate "tablets" or "no major changes" (for ≤10 years and 11-20 years: OR = 0.5; 95% CI: [0.3-0.8]; *P* = 0.02). There was no significant association with age, place of employment, membership of ETA/ATA or number of patients treated annually.

Monitoring thyroid hormone treatment

After initiating LT4 treatment or switching to another formulation / another manufacturer, most responders stated that they would measure serum TSH after 8 weeks (268/535 (50.1%) and 274/535 (51.2%) respectively) or after 4-6 weeks (220/535 (41.1%) and 196/535 (36.7%), respectively). TSH measurement after 2 weeks was chosen by only 4/535 responders (0.7%) after initiating LT4 and none after switching of formulation or manufacturer. Only 9/535 (1.7%) responders stated that they relied on clinical evaluation alone after a switch to another formulation or manufacturer to assess adequacy of thyroid hormone replacement.

Male physicians and physicians treating fewer than 100 patients per year were less likely to monitor TSH after 8 weeks in comparison with the other options, which comprised: "after 2 weeks", "after 4-6 weeks", "on the basis of clinical evaluation" (OR for males = 0.5; 95% CI: [0.3-0.8]; *P* = 0.002; OR for 51-100 patients = 0.6; 95% CI: [0.4-0.9]; OR for 10-50 per year = 0.3; 95% CI: [0.2-0.5]; *P* = 0.0001). Moreover, responders who practiced exclusively in the public sector (University Center, Regional Hospital, Research) were also less likely to monitor TSH after 8 weeks in comparison with the other options (OR = 0.6; 95% CI: [0.4-0.8]; *P* = 0.001).

Treating euthyroid patients with thyroid hormones

Circumstances under which physicians would consider thyroid hormones for euthyroid patients are shown in Figure 1. Responders were allowed to select one or more of several options. Among 535 responders, there were 43 missing data. Responders were nearly equally divided between two answers: 216/492 (44.0%) stated that thyroid hormones are never indicated in euthyroid patients and 198/492 (40.2%) would consider thyroid hormones for euthyroid patients with simple goiter growing over time. Among responders who chose the latter option, 59/198 (29.3%) were aged over 60 years and 29/198 (5.4%) were under 40 years. ($P < 0.0001$) Finally, 156/492 (31.7%) responders would consider treatment with thyroid hormones in women with positive anti-thyroperoxidase antibodies (TPO Abs) and infertility. Multivariate analysis showed that exclusive public practice was the only parameter associated with unwillingness to prescribe thyroid hormones for euthyroid patients (OR: 1.6 [1.1-2.4]; $P = 0.007$).

Combination treatment with LT4 + LT3

Most members (n = 305/535; 57%) would never consider combination treatment with LT4 + LT3 due to the low quality of evidence supporting their use. In case of persistent symptoms of hypothyroidism despite normal TSH, 139/535 (26%) would consider switching from LT4 to LT4+LT3. Among them 86/139 (62%) worked in private practice. Other indications (unexplained weight gain or for a short period, in patients recovering from protracted hypothyroidism) were rarely considered by only 1/535 (0.2%) and 47/535 (8.8%) of responders, respectively, while 43/535 (8%) members did not respond to this question.

There was an association between being exclusively in public service and non-use of combination treatment with LT4+LT3, compared to responders in private practice (OR = 1.4 ; 95% CI: [1-2]; $P = 0.05$).

Persistence of symptoms of hypothyroidism despite normal serum TSH during LT4 treatment

Most responders considered that persisting symptoms of hypothyroidism, despite normal serum TSH during LT4 treatment, is a rare problem affecting fewer than 5% of patients for 168 (31.4%) out of 535 responders and between 6-10% of patients for 180 (33.7%) out of 535 responders. Only 8 out of 535 (1.5%) responders considered that this problem affects more than 30% of treated patients. Most members 223/535 (41.7%) estimated that this problem has remained stable or has decreased 74/535 (13.8%) over the past five years, while 93/535 (17.4%) considered that its frequency has increased. A total of 145/535 (27.1%) responders did not answer the question or were not sure of the tendency over the past 5 years.

Responders aged over 60 years were likely to answer that persisting symptoms of hypothyroidism despite normal serum TSH during LT4 treatment is a rare problem affecting less than 10% of patients (when ≤40 years was set as reference, OR for >60 = 2.1; 95% CI [1.2-3.7]; P = 0.04). Other variables (sex, age, years in medical practice, place of employment, membership of ETA/ATA and the number of patients treated annually) were not associated with responses to this question.

FES members were asked about possible explanations of persistent hypothyroid symptoms in patients with normal TSH (Figure 2). Psychosocial factors, chronic fatigue syndrome, the burden of chronic disease, comorbidities and patients' unrealistic expectations were the most frequent explanations selected by the responders.

Supplementation with selenium and iodine

FES members were almost equally divided between two answers regarding selenium and iodine supplementation: 204/535 (38.1%) answered that such supplements should never be used and 167/535 (31.2%) would consider these supplements upon the patients' request. Some would consider selenium or iodine in case of subclinical

hypothyroidism (N = 67/535; 12.6%) or in patients with co-existing autoimmune thyroiditis (N = 54/535; 10.1%). Among 535 responders 43 did not answer the question.

Male responders and those over 60 years or exclusively in public practice were more likely to never consider selenium or iodine supplementation (OR for male = 2.3; 95% CI [1.5-3.4]; *P* = 0.0001; when 40 years old is set as 1, OR for >60 = 1.9; 95% CI: [1.1 -3.2]; *P* = 0.03; OR for public practice = 1.5; 95% CI: [1.04-2.1]).

French Endocrine Society members with hypothyroidism

Among 535 responders 39 (7.3%) declared that they had a diagnosis of hypothyroidism. Only 4 experiencing excessive tiredness and 2 declared that they had tried combination therapy with LT4+LT3.

Among 535 responders 453 (84.7%) claimed not to be diagnosed with hypothyroidism (43 did not provide an answer to this question). To the question "Would you consider combination therapy with LT4+LT3 or desiccated thyroid extract if you were diagnosed with hypothyroidism?" 42/453 (9.3%) responders answered affirmatively. Of 139 responders who had stated that they would consider combination treatment for hypothyroid patients with persistent symptoms, only 38 would treat themselves with combination treatment if they found themselves in that predicament.

Discussion

Around a quarter of the FES members and of the affiliated societies completed the survey. More than 95% were practicing endocrinologists, which suggests that the results reflect real-life practice in France. The typical respondent was female between 40 and 60 years, with at least 11 years experience in medical practice, half

of whom worked exclusively in public practice. The majority of respondents treated hypothyroid patients frequently, 57.2% stated that they treated more than 100 hypothyroid patients per year.

Treatment with LT4

This survey demonstrated that LT4 is the treatment of choice by French specialists for newly diagnosed hypothyroid patients, in accordance with European (10, 11) and American guidelines (12). Several formulations of LT4 are available in France, including soft-gel capsules and liquid solutions, along with different brands or generic for LT4 tablets. However, LT4 tablets remain the preferred formulation even in specific situations such as taking interfering drugs, suspicion of malabsorption, poor biochemical control, and persistent symptoms of hypothyroidism despite normal TSH level. It can be hypothesized that the absence of robust cost-effectiveness data regarding the use of these alternative formulations is an explanation for their limited use in France (4). Other possible explanations relate to reimbursement by the French insurance system of LT4 tablets (brands or generic) but not soft-gel capsules (Tcaps®) or some liquid solutions (Tsoludose®), and persistent prescribing habits as these alternative formulations have been made available only recently (since 2018).

However, the non-negligible proportion of physicians who would consider soft-gel capsules in case of gastrointestinal issues (suspicion of malabsorption, lactose intolerance or intolerance to excipients) and in case of poor biochemical control, 19.8% and 18.1%, respectively, is notable, despite the absence of robust cost-effectiveness data.

One issue which may have impacted the responses to the survey, concerns the different brands of LT4 tablets available in France. This is a consequence of the release in March 2017, at the request of French authorities, of a new formulation of

Levothyrox®, with the objective of avoiding stability deficiencies of the old formulation (13). Unfortunately, probably due to inadequate communication with physicians and patient organizations regarding the formulation changes, several thousands of patients reported adverse drug reactions following this replacement. Moreover, the bioequivalence of the new and old formulations has been questioned (14). One of the long-term actions taken by the French Ministry of Health, consequently, was to make available to French patients who request it, two other brands of LT4, L-thyroxin Henning® (Sanofi) and Thyrofix® (Unifarm). Notably a position statement on the interchangeability of LT4 products recommends that patients should be maintained on the same formulation/brand name of LT4 and to monitor serum TSH after 6 weeks if a change is necessary (13). Moreover, French Health Authorities had stated at that time that liquid formulation was primarily intended for infants and children, in a context of a shortage risk of this formulation, which can explain its relative limited use for adult patients in France.

In this survey, 90% of the responders would measure serum TSH within 4 to 8 weeks after starting LT4 or switching from one formulation to another or from a branded to a generic product, as recommended by current guidelines (10-12).

Thyroid hormones in euthyroid patients

In accordance with current guidelines (9-12) a significant proportion (40.4%) of responders would never consider thyroid hormone treatment in euthyroid patients. A similar proportion of responders (37%) stated that they would consider thyroid hormones in a euthyroid patient with a goiter growing over time despite the limited efficacy in terms of size reduction of TSH suppressive LT4 treatment (15, 16), along with the potential side effects of subclinical thyrotoxicosis (17, 18). This outdated practice was rare among young physicians i.e. under 40 years (5.4%) compared to physicians over 60 years (29.3%).

A significant minority (almost a third) of responders would consider thyroid hormone treatment in a euthyroid female with infertility associated with TPO Abs, despite the recent publication of a large prospective randomized clinical trial refuting any benefit of LT4 treatment in this indication (19). These results parallel that found in previous Italian (20), Danish (21), Spanish (22), Polish (23) and Romanian (24) THESIS surveys while this practice is less frequent in Bulgaria (25). A consensus regarding the management of goiter is currently being drafted under the aegis of the FES and will partially address these improper practices in France.

Combination therapy with LT4+LT3

Fourteen clinical trials have not shown a consistent benefit of combination therapy with LT4+LT3 (26), however in clinical practice only 57% members of the French Endocrine Society stated that they would never consider this treatment, with a similar trend in other European Countries (20, 21). Most of the responders who would consider combination treatment with LT4+LT3 would do so for persistent symptoms of hypothyroidism despite adequate biochemical control (26%). Prescription of these LT3-based preparations remains a subject of debate in the endocrine community and the role of alternative reasons for the impact on quality of life, such as comorbid conditions and the socio-economic consequences of hypothyroidism – whether adequately treated or not – needs more attention (8, 27-31). Some argue that in some randomized control trials comparing LT4+LT3 combination with LT4 monotherapy, the majority of patients preferred LT4+LT3 therapy, even if the explanation for this preference remains to be elucidated (32). Interestingly a consensus document to guide development of future clinical trials of LT4+LT3 combination therapy was recently published (33). The results of such trials are expected to be of benefit to patients and of value to inform future thyroid hormone replacement clinical practice guidelines treatment recommendations (33).

Supplementation with iodine and selenium

There are no French national guidelines regarding the supplementation with iodine and selenium. In line with the lack of recommendations, the responders were divided, stating that either dietary supplements should never be used (38.1%) or that they could be used at the request of the patients (31.2%). Iodine fortification of salt was implemented in France in 1952, initially set at 10-15 mg/kg, then increased to 15-20 mg/kg in 2002. Nowadays in France, only pregnancy remains a period at risk of mild or moderate iodine deficiency (34, 35). Nonetheless, the benefit of iodine supplementation for hypothyroid patients has not been demonstrated. Regarding selenium supplementation, a recent review concluded that - despite of an effect on thyroid antibodies (36) - there is no evidence of clinical benefit by selenium supplementation in patients with autoimmune thyroiditis (37).

Treatment of physicians with hypothyroidism

Interestingly, of the responders affected by hypothyroidism only 9.3% would consider combination therapy with LT4+LT3 for themselves, while 35% of them would consider it for their patients. This discrepancy remains unexplained but might suggest that patients may pressurize physicians to provide treatments that they believe will improve their QoL, while physicians favor alternative explanations for persistent symptoms. Analyzing the aggregate data from respondents from 28 participating countries in the THESIS studies will shed more light on this intriguing contradiction.

Strengths and Limitations

The strength of this survey is the relatively high response rate, as compared to similar others (20-25, 38) and being part of a large European survey that has collected data from thousands of physicians. Besides the strength came also from having data from the private and the public sector and thereby covering a real-life situation in France and possibly all the key opinion leaders.

One of the limitations is that LT4 treatment in France is initiated mainly by general practitioners (2) who were not represented in the survey, as virtually all responders (97.2%) were physicians. Another limitation is related to the virtual patient scenarios and that the medical decision incorporating the patient's wishes and point of view was not considered in the survey.

To conclude, in France the treatment of choice for hypothyroidism is LT4 and the principal formulation of choice is tablets. LT3-based preparations are considered by a minority of physicians, primarily for persistent symptoms of hypothyroidism despite normal TSH concentration. Most physicians would never consider thyroid hormones in euthyroid patients. Alternative formulations, such as soft-gel capsule or liquid solution would be considered by a minority of physicians, especially in case of gastrointestinal issue and poor biochemical control of the disease. The attitude of French specialists towards selenium and iodine supplementation in hypothyroidism is variable reflecting ongoing uncertainties of the evidence base.

Figures and Table

Table 1

Gender	n (%)

Male	133 (24.9)
Female	402 (75.1)
Age in years	
≤ 40	150 (28)
40-60	263 (49.2)
>60	122 (22.8)
Years in medical practice	
≤ 10	116 (21.7)
11-20	139 (26)
21-30	134 (25)
> 30	146 (27.3)
Specialty[a]	
Endocrinology	520 (97.2)
Internal Medicine	20 (3.7)
Others	49 (9.1)
Nationality	
French	528 (98.7)
Belgian	2 (0.4)
Swiss	5 (0.9)
Place of employment[a]	
University Center	225 (42.7)
Regional Hospital	125 (23.4)
Private Clinic	46 (8.6)
General practice	2 (0.4)
Private Practice	136 (25.3)
Research	1 (0.2)
Public versus private practice[b]	
Exclusive public practice	274 (51.2)

Private practice	261 (48.8)
Frequency of management of patients with thyroid disease	
Daily	351 (65.6)
Weekly	165 (30.8)
Rarely	19 (3.6)
Frequency of management of patients with hypothyroidism	
> 100 patients/year	305 (57.2)
51-100 patients/ year	149 (28)
10-50 patients/ year	75 (14.1)
Rarely	6 (0.7)

[a] The sum of percentages exceeds 100% because some responders had >1 specialty and had more than one employment.

Table 2

	Tablets n (%)	Soft gel capsules n (%)	Liquid solution n (%)	I expect no major changes with the different formulations n (%)	Missing data n (%)
Interfering drugs may influence the stability of therapy. Which LT4 preparation is in your experience less likely to be subject to variable absorption?	93 (17.4)	61 (11.4)	35 (6.5)	303 (56.7)	43 (8)
Which of the following preparations of LT4 would you prescribe in case of a 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 excipients?	160 (30)	106 (19.8)	69 (12.9)	157 (29.3)	43 (8)
Which of the following preparations of LT4 would you prescribe for a patient established on LT4 who has unexplained poor biochemical control of hypothyroidism?	184 (34.4)	97 (18.1)	33 (6.2)	178 (33.3)	43 (8)
Which of the following preparations of LT4 would you	142 (26.5)	86 (16.1)	30 (5.6)	234 (43.8)	43 (8)

prescribe for a patient with poor biochemical control who is unable (due to busy lifestyle) to take LT4 fasted and separate from food/drink?					
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?*	166 (33.2)	36 (7.2)	10 (1.9)	245 (49)	43 (8)

* 35 responses were excluded because more than one answer was provided.

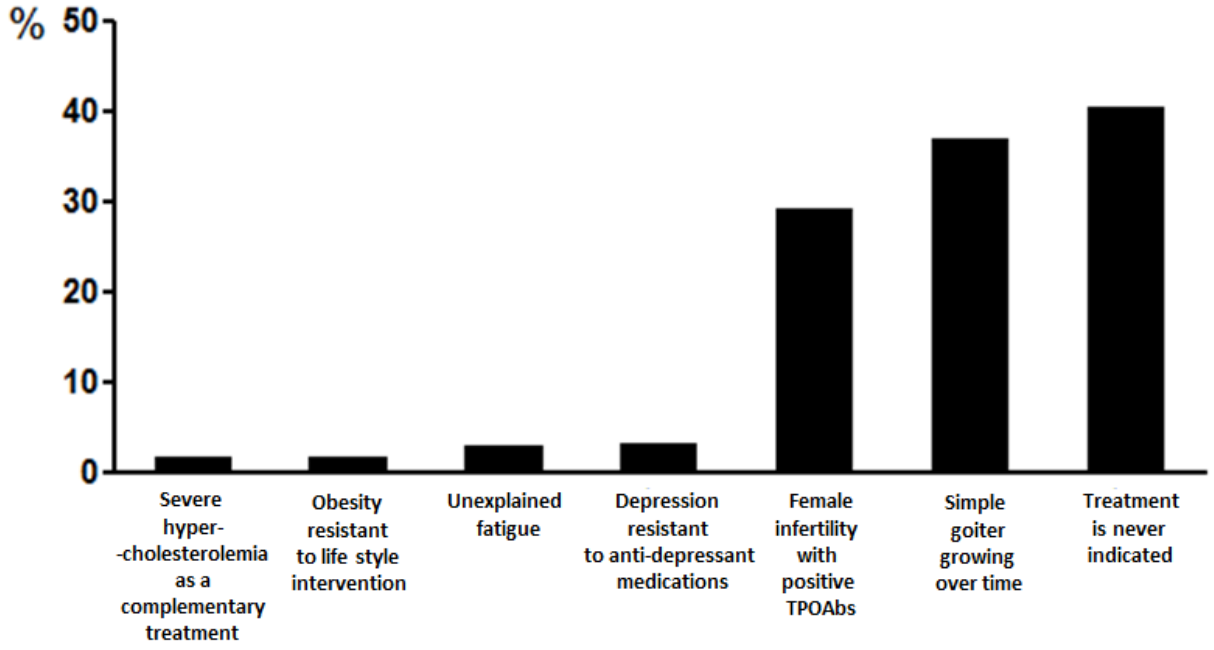

Figure 1

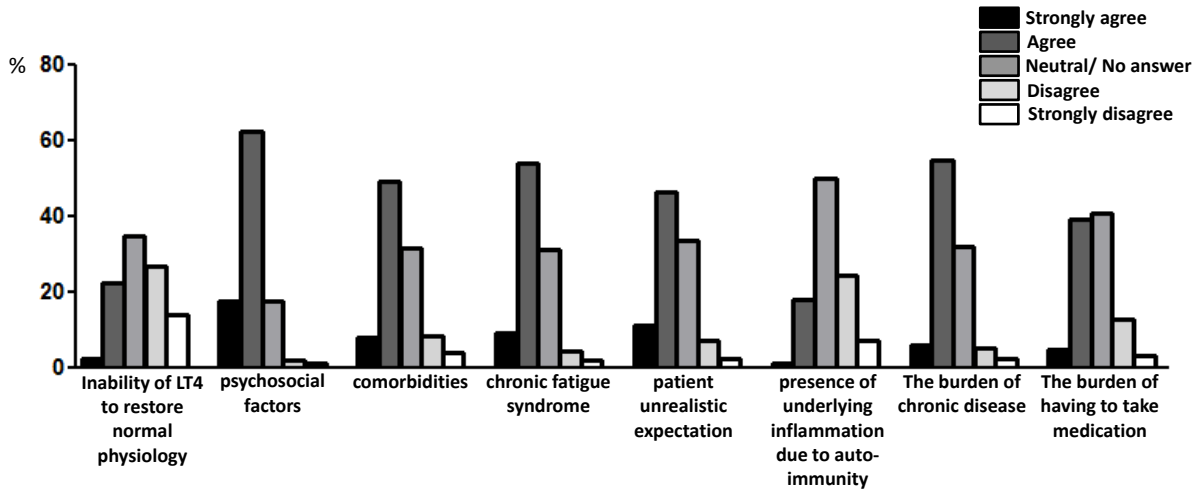

Figure 2

Table and Figure : Legends

Table 1. Characteristics of the 535 responders

Table 2. LT4 formulations preferred by responders in different clinical scenarios

Figure 1. Putative indications for thyroid hormone treatment in biochemically euthyroid patients. TPO Abs = Thyroperoxidase Antibodies; *NB: Excluding those who replied that treatment is never indicated, the remainder could select more than one answers*

Figure 2. French Endocrine Society members' speculation regarding possible factors explaining persistent symptoms of hypothyroidism despite biochemical euthyroidism in patients treated with LT4.

Supplementary Material : Legends

Supplementary Material 1 The THESIS survey

Supplementary Material 2 Flow chart of the French THESIS survey.* Data from the French National Medical Council (2020)

Supplementary Material 3. Factors associated with the prescription of LT4 alone or alternatives (LT4+LT3, LT3 or dessicated thyroid extracts)

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Conflicts of interest

Camille Buffet has been lecturer without fees for Merck Serono SAS.

Laurence Leenhardt has received consulting fees for Merck, research funding from Merck Serono SAS (Lyon, France) and honoraria for lectures from Laboratoires Genevrier (Antibes, France).

Laszlo Hegedüs, Petros Perros, Endre Nagy and Enrico Papini are consultants for and scientific board members of IBSA Institut Biochimique. They have received fees from IBSA Institut Biochimique.

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