Endocrinología, Diabetes y Nutrición 69 (2022) 520–529

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

ORIGINAL ARTICLE

Use of thyroid hormone in hypothyroid patients and euthyroid subjects in Spain: A THESIS* questionnaire survey☆

Juan C. Galofré[a,b,c,*], Roberto Attanasio[d], Laszlo Hegedüs[e], Endre Nagy[f], Roberto Negro[g], Enrico Papini[h], Petros Perros[i], Juan J. Díez[c,j,k,l]

[a] *Department of Endocrinology, Clínica Universidad de Navarra, Pamplona, Spain*
[b] *Instituto de Investigación Sanitaria de Navarra (IdiSNA), Spain*
[c] *Thyroid Task Force from the Sociedad Española de Endocrinología y Nutrición (SEEN), Madrid, Spain*
[d] *IRCCS Orthopedic Institute Galeazzi, Endocrine Unit, Milan, Italy*
[e] *Department of Endocrinology and Metabolism, Odense University Hospital, Odense, Denmark*
[f] *Division of Endocrinology, Department of Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary*
[g] *Division of Endocrinology, V. Fazzi Hospital, Lecce, Italy*
[h] *Department of Endocrinology and Metabolism, Regina Apostolorum Hospital, Rome, Italy*
[i] *Department of Endocrinology, Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom*
[j] *Department of Endocrinology, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain*
[k] *Instituto de Investigación Sanitaria Puerta de Hierro Segovia de Arana, Majadahonda, Madrid, Spain*
[l] *Department of Medicine, Universidad Autónoma de Madrid, Spain*

Received 18 May 2021; accepted 8 July 2021

KEYWORDS
Hypothyroidism;
Thyroid hormone;
Treatment;
Survey

Abstract
Background: Hypothyroidism is one of the leading conditions in endocrinology. Despite that fact, clinical indications for treatment still vary among Spanish specialists.
Aims: To identify attitudes of Spanish specialists relating to the use of levothyroxine (LT4) and the management of hypothyroidism.
Methods: The members of the *Sociedad Española de Endocrinología y Nutrición* (Spanish Society of Endocrinology and Nutrition) were invited to participate in a web-based survey. The survey, initially in English, was modified to reflect in accordance with the availability of thyroid hormone formulations in Spain.
Results: A total of 505 of 1956 (25.8%) members (66% female) completed the survey; 97.4% declared that LT4 is the first-line therapy for hypothyroidism. The indications for LT4 therapy in euthyroidism were infertility in thyroid antibody-positive women (48.5%) and simple goitre (21.2%). However, 44.2% of specialists reported that there was no indication for LT4 therapy in such patients. Only a minority of respondents (2.6%) considered combining LT4 with liothyronine as the treatment of choice from inception, whereas 49% stated that it should never be used.

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

* Corresponding author.
E-mail address: jcgalofre@unav.es (J.C. Galofré).

Conclusions: The standard of treatment of hypothyroidism in Spain is almost exclusively with LT4 tablets. Availability of other formulations of LT4 or combination therapy for hypothyroidism management remains to be explored, especially in patients with persistent symptoms. Notably, non-evidence-based use of LT4 is widely practiced in Spain for euthyroid women with autoimmune thyroiditis and fertility issues.

PALABRAS CLAVE
Hipotiroidismo;
Hormona tiroidea;
Tratamiento;
Encuesta

Uso de la hormona tiroidea en pacientes hipotiroideos y sujetos eutiroideos en España

Resumen
Antecedentes: El hipotiroidismo es una de las principales afecciones en endocrinología. No obstante, las indicaciones de tratamiento varían entre los especialistas españoles.
Objetivos: Identificar las actitudes de los especialistas españoles en el manejo del hipotiroidismo y el empleo de la levotiroxina (LT4).
Métodos: Se invitó a los miembros de la Sociedad Española de Endocrinología y Nutrición a participar en una encuesta *on line*. La encuesta, originalmente en inglés, se modificó para reflejar la disponibilidad de formulaciones de hormonas tiroideas en España.
Resultados: De los 1.956 socios, 505 (25,8%; 66% mujeres) completaron la encuesta. El 97,4% declaró que LT4 es la terapia de primera línea para el hipotiroidismo. Las indicaciones del tratamiento con LT4 en el eutiroidismo fueron infertilidad en mujeres con anticuerpos antitiroideos positivos (48,5%) y bocio simple (21,2%). Sin embargo, el 44,2% de los especialistas contestó que no había indicación de tratamiento con LT4 en estos casos. Solo una minoría (2,6%) consideró que la combinación de LT4 con liotironina era el tratamiento de elección desde el inicio, mientras que el 49% afirmó que nunca debería usarse.
Conclusiones: El tratamiento convencional del hipotiroidismo en España es casi exclusivamente mediante comprimidos de LT4. Actualmente no hay disponibilidad de otros preparados de LT4. La terapia combinada, especialmente para aquellos pacientes con síntomas persistentes de hipotiroidismo, no ha sido aún explorada. Aunque su uso no esté basado en la evidencia, en España se prescribe ampliamente LT4 en mujeres eutiroideas con tiroiditis autoinmune y problemas de fertilidad.

Introduction

Hypothyroidism is one of the most prevalent endocrine conditions worldwide, including in Europe.[1,2] According to the major international guidelines,[3,4] replacement treatment with levothyroxine (LT4) is the conventional treatment for this condition. It is, apparently, simply to manage it. However, real-life practice involves dealing with a large number of patients with normal serum thyrotropin (TSH) levels who yet exhibit persistent hypothyroidism-like related symptoms. This apparently suboptimal control of hypothyroidism may lead attending physicians to explore alternative strategies to satisfy patients' requirements. In addition, there are some non-conventional indications for LT4 therapy (not supported by evidence) in euthyroid subjects. Among them are infertility, hypercholesterolemia, depression, obesity and goitre.[5–7]

In contrast with other European countries, the only approved thyroid replacement formula in Spain is LT4 tablets, aside from the seldom-prescribed intravenous solution used in emergencies.[8] The Spanish public healthcare system, or its regional counterpart in each of the country's 17 autonomous regions, usually funds this treatment. The Spanish market is almost entirely controlled by one of the three name brands of levothyroxine available. Generic levothyroxine is seldom prescribed due to the low cost of its name brand. In selected cases, imported thyroid hormone preparations, such as combination therapy with tablets with LT4 and liothyronine (LT3), may be approved after adequate justification to health authorities.

There are no National hypothyroidism guidelines supported by the *Sociedad Española de Endocrinología y Nutrición* (SEEN), apart from management of subclinical hypothyroidism during pregnancy.[9] Therefore, current practice is based mainly on the recommendations of international scientific societies.[3,4,10] Although Spanish endocrinologists routinely see many patients with underactive thyroid conditions, most hypothyroid patients are, in fact, identified and treated by a general practitioner.[11]

In recent years, new data have emerged, leading to an increased interest in exploring innovative measures to improve the quality of life of hypothyroid patients,

especially that of patients dissatisfied with their treatment outcome.[12–15] However, the physicians' perspective has not been explored extensively. For this reason, the THESIS (Treatment of Hypothyroidism in Europe by Specialists: an International Survey) project was developed. It is an ambitious pan-European survey aimed at identifying the current attitudes of specialists involved in the treatment of hypothyroidism.[16]

This survey aimed to assess the current attitudes of Spanish members of the SEEN towards the conventional treatment of hypothyroid patients with LT4 and the non-conventional use of LT4 in euthyroid subjects in their daily clinical practice.

Methods

Survey design

Each THESIS questionnaire was in both Spanish and English. Two of the co-authors (JJD and JCG) translated the original English text into Spanish (Supplementary Material, Table S1). Questions B3 and B6-B9 of the initial survey were not included because they have to do with thyroid hormone preparations commercially unavailable under the Spanish healthcare system.

Ethical issues

The SEEN board of directors and its Thyroid Task Force Steering Committee approved the study. The participants were not asked for any personal data that could make possible their identification to ensure anonymity.

Dissemination

The survey was posted on the SEEN webpage, available to all members ($n = 1956$) from September 10 to November 18, 2020. Invitation e-mails were sent to members immediately before initiating the survey (September 10, 2020). Two monthly reminders mailings were subsequently sent, one in October and another in November. Participant responses were electronically compiled, saved and hosted on an open-access form creation website (https://www.google.com/forms/). Only the authors had access to the survey database.

Statistical analysis

Categorical variables are described as absolute values and percentages. As not every participant 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. Responses to the only question in which respondents were asked to give their opinion on a scale of 1–8 to reflect the possible cause of symptoms persistence in those patients with normal serum TSH are expressed as median and interquartile range. Chi-square tests and Fisher's exact tests were used to compare proportions. Differences were considered significant when $P < 0.05$.

Results

Surveyed physicians

We obtained 512 responses, representing approximately a quarter of the 1956 SEEN members, of whom 90% are physicians and the remainder 10% basic investigators. After the exclusion of 7 incomplete questionnaires, 505 valid responses were analysed. Two-thirds (66%; 333/505) of those who responded were female, and 57% (288/505) of the participants have been practising for less than 20 years. Almost all were endocrinologists who performed a large proportion of their work at university hospitals. Most participants deal with thyroid patients daily, with 70% treating more than 100 hypothyroid patients per year (Table 1).

Indication of thyroid hormones in euthyroid subjects (non-conventional use of LT4)

The respondents' main indication for LT4 treatment in biochemically euthyroid subjects (non-conventional use of LT4) was female infertility with a high level of thyroid antibodies (48.5%), followed by the presence of a slow-growing simple goitre (21.2%). In contrast, 44.2% stated that thyroid hormone is never indicated for biochemically euthyroid subjects (Table 2).

Treatment hypothyroid patients with thyroid hormones (conventional)

Most respondents (97.0%; 490/505); stated that LT4 was the first-line replacement therapy for hypothyroid patients (conventional use). Only 13 respondents (2.6%) were in favour of combination therapy (LT4 + LT3). Four hundred and sixty-six (92.5%) answered that most of their patients took the LT4 brand they had prescribed, while general practitioners changed the brand in 4% of cases, with the remaining 3% stating that they had no control over the specific brand of LT4 eventually taken by patients. Only 0.4% acknowledge that they had to justify the brand of LT4 to the regulatory authorities. Almost half of the sample (238/491; 48.5%) considered LT4 tablet to be the preparation least likely to be subject to variable absorption (among a selection of alternative formulations) due to interference with other medications. Only 6.5% and 3.3% believed that the preparations least at risk of a variable absorption are liquid solution and soft-gel capsules, respectively. Moreover, 41.8% did not expect significant absorption changes between the different formulations.

Control of serum TSH during therapy

Once treatment was initiated, the preferred timing of first control of serum TSH was carried out at 4–6 weeks and 8 weeks by 40.4% and 59.2% of respondents, respectively. If the LT4 formula or brand was switched, 47.7% of surveyed physicians recommended checking serum TSH at 8 weeks, with 25.7% checking TSH levels at 4–6 weeks. Only 10.5% relied on clinical evaluation, and 16.0% indicated that there

Table 1 Characteristics of the 505 respondents.

	N (%)
Gender	
Male	169 (33.5)
Female	333 (65.9)
Unknown	3 (0.6)
Years in medical practice	
≤20	288 (57.0)
21–40	187 (37.0)
>40	17 (3.4)
Unknown	13 (2.6)
Specialisation[a]	
Endocrinology	493 (97.6)
Internal Medicine	17 (3.4)
Family Medicine	9 (1.8)
Others	6 (1.2)
Place of employment[a]	
University hospital	381 (75.4)
Regional hospital	90 (17.8)
Private clinic	51 (10.2)
General practice	3 (0.6)
Specialist practice	64 (12.7)
Membership[a]	
SEEN	449 (88.9)
ETA	14 (2.8)
ATA	4 (0.8)
LATS	1 (0.2)
None	50 (9.9)
Frequency of management of patients with thyroid disease	
Daily	432 (85.5)
Weekly	67 (13.3)
Rarely	2 (0.4)
Unknown	4 (0.8)
Frequency of management of patients with hypothyroidism	
10–50 patients/year	45 (8.9)
51–100 patients/year	101 (20.0)
>100 patients/year	357 (70.7)
Rarely	1 (0.2)
Unknown	1 (0.2)

Abbreviations: SEEN, Spanish Society of Endocrinology and Nutrition; ETA, European Thyroid Association; ATA, American Thyroid Association; LATS, Latin American Thyroid Society.

[a] The sum of percentages exceeds 100% because some respondents had >1 specialty and had more than one employer and/or were members of more than one scientific society.

was no need to monitor TSH following a change in LT4 formulation or manufacturer.

Use of dietary supplements and a combination of LT4 and LT3

More than a third of the participants (188/495; 38.0%) responded that dietary supplements could be used in addition to thyroid hormone replacement upon patient request or as a complementary treatment. Subclinical hypothyroidism and the coexistence of autoimmune thyroiditis were

Table 2 Respondents' opinion on the indications of thyroid hormones in biochemically euthyroid subjects.

	N (%)[a]
Unexplained fatigue	20 (4.0)
Obesity resistant to life-style interventions	12 (2.4)
Severe hypercholesterolemia, as a complementary treatment	21 (4.2)
Depression resistant to anti-depressant medications	29 (5.7)
Female infertility with high level of thyroid antibodies	245 (48.5)
Simple goitre growing over time[b]	107 (21.2)
Thyroid hormone is never indicated for these patients	223 (44.2)

[a] The sum of percentages exceeds 100% because some respondents can answer yes to various indications.

[b] Respondents were instructed «If this is ever an indication, even under specific circumstances (e.g., taking into account age and comorbidities) then it should be ticked».

Table 3 Perceptions about the occurrence of persistence of hypothyroid symptoms despite normal serum TSH.

	Number (%)[a]
Frequency	
<5%	175 (34.7)
6–10%	175 (34.7)
11–30%	107 (21.2)
More than 30%	16 (3.2)
Not sure	31 (6.2)
Trends	
I am seeing more such cases	136 (26.9)
I am seeing fewer such cases	37 (7.3)
No change	272 (53.9)
Not sure	60 (11.9)

[a] Number of valid responses in the question about frequency: 504; number of valid responses in the question about trends: 505.

conditions for which dietary supplements were prescribed in 16.4% and 14.1% of the cases, respectively. In contrast, 31.5% of specialists stated that dietary supplements should never be prescribed.

Almost half of the respondents (49%) believed that combination replacement therapy (LT4 and LT3), a formula not marketed in Spain, should never be used, whereas 40% of participants answered that it could be an option for patients who continued to complain of hypothyroid symptoms despite being biochemically euthyroid.

Persistence of symptoms despite normal TSH

Participants were surveyed about LT4-treated hypothyroid patients who continued to experience symptoms despite normal serum TSH levels. According to more than two-thirds of respondents, the frequency of this phenomenon was present in 10% or less, with a trend unchanged over time (Table 3). More than 60% of respondents agreed or strongly

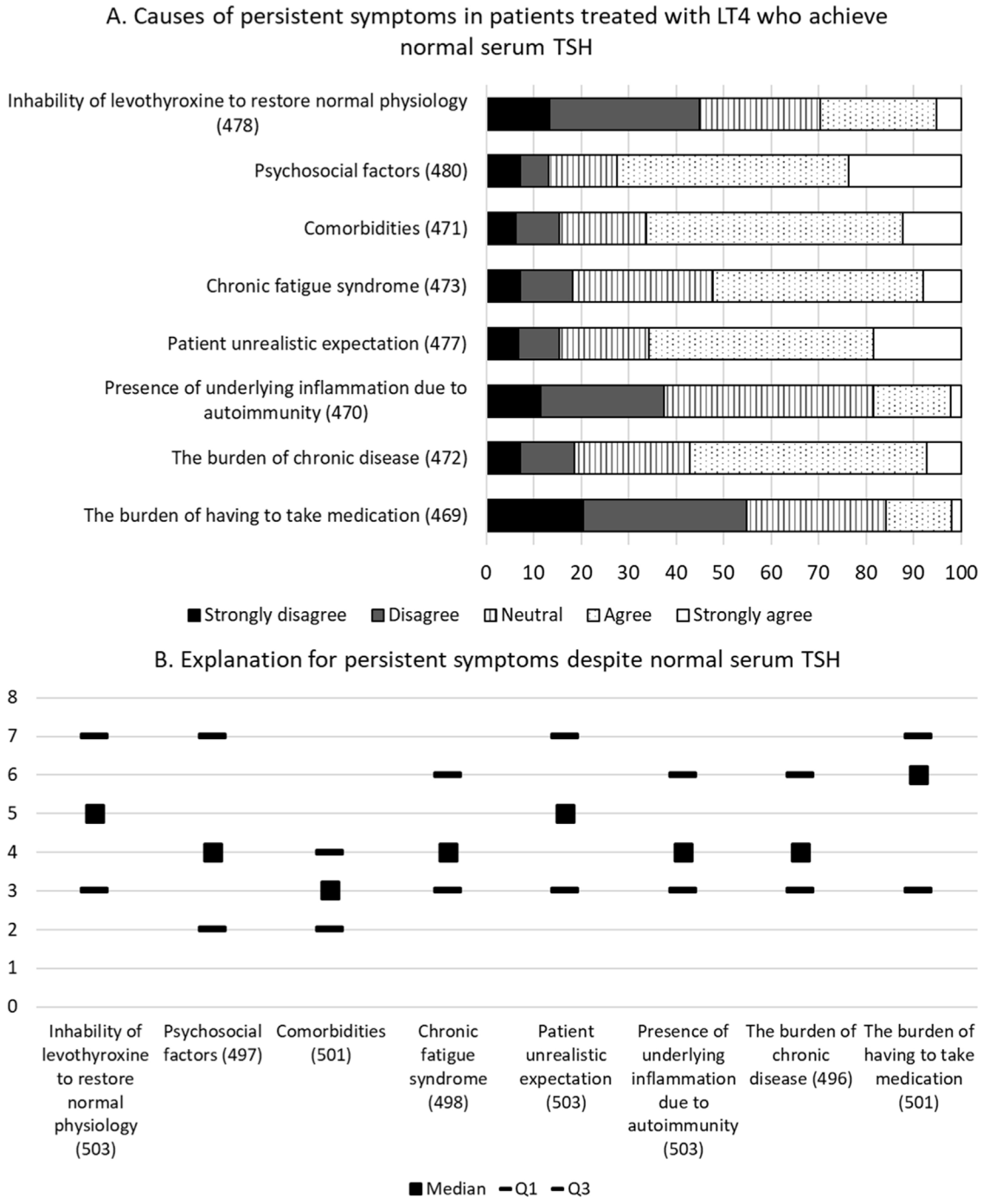

Figure 1 (A) Opinion of respondents on the causes of persistent symptoms in patients treated with LT4 who achieved normal serum TSH. Physicians provided their opinion on the different requested issues (strongly disagree, disagree, neutral, agree and strongly agree). (B) Experience of respondents with patients treated with LT4 who achieved normal serum TSH but continued to experience symptoms such as fatigue. Respondents were asked to rank each factor from 1 to 8, where 1 is the most likely and 8 the least likely explanation in their opinion. The data are the median (squares) and the interquartile range (horizontal lines). Figures in brackets indicate the number of interviewees who responded to each of the items.

agreed that these persistent symptoms could be explained by psychosocial factors (72.6%), comorbidities (66.2%) or unrealistic patient expectations (65.8%). More than 40% of participants were confident of the ability of LT4 to restore patients to their normal physiology (Fig. 1A).

Participants were asked to rank, according to their experience, the relevance of possible explanations for persistent symptoms in patients who achieve normal serum TSH. The range was from 1 to 8, where 1 was the most likely and 8 was the least likely reason (Fig. 1B). The explanations considered least likely by respondents were the inconvenience of taking medication, followed by unrealistic patient expectations and the inability of LT4 to restore the patient to normal physiology.

Hypothyroid physicians' choice

Fifty-one respondents (10.1%) acknowledged having hypothyroidism themselves, of which 13 (25.5%) reported experiencing excessive tiredness or fatigue. Five hypothyroid physicians (9.8%) had tried LT4 and LT3 combination therapy, and one (2.0%) had tried desiccated thyroid treatment.

Lastly, 76 out of 439 (17.3%) non-hypothyroid physicians stated that they would consider LT4 and LT3 combination therapy or desiccated thyroid for themselves if they developed hypothyroidism.

Subgroup analysis

We examined various items to explore associations between the respondents' baseline characteristics, such as gender, years in practice, hospital affiliation (academic or non-academic) on the one hand, and the volume of hypothyroid patients they dealt with on the other (Table 4).

The most important factors of these were years in practice and the volume of patients per year. The longer the respondents had been in practice, the more likely they considered that there was no indication for treatment in biochemically euthyroid subjects and the more reluctant they were to prescribe dietary supplements. Furthermore, compared to younger physicians, more experienced specialists (with a practice longer than 20 years) were predisposed to believe that comorbidities or psychosocial factors were the leading causes of persistent hypothyroidism-like symptoms in subjects with normal TSH. Specialists who deal with more than 100 patients per year were more inclined to prescribe LT4 in female infertility cases and use combined treatment with LT4 and LT3 in patients with persistent symptoms. The institution (either university or non-academic hospital) had no influence over the opinion of the respondents.

Discussion

Around a quarter of the SEEN members completed the survey. More than 90% of they are practicing endocrinologists, which suggests that the results reflect the real-life practice in Spain. The typical respondent was a young female doctor working in an academic institution (75% from a university hospital). Nevertheless, no relationship was found between the type of hospital (academic or otherwise) of the respondent and the treatment prescribed for hypothyroidism.

The survey analysed respondents' opinions about LT4 treatment indications in conventional (patients with an underactive thyroid or without a thyroid gland) and non-conventional (patients with hypothyroid-like symptoms with normal serum thyroid hormone levels) conditions. It also assessed Spanish physicians' attitude towards the (apparently adequately) supplemented hypothyroid patient (with normal thyroid hormone levels) who continued to complain about symptoms traditionally associated with hypothyroidism.

The only replacement therapy for hypothyroidism available in Spain is LT4 in tablets.[8] The Spanish National Health Service (NHS), which covers the country's entire population, provides funding for the drug. As previously mentioned, combination treatment (LT4 + LT3) or liothyronine alone are not available on the national market, although a request may be made to the national health service. Other formulas such as LT4 in soft-gel capsules and liquid solutions or desiccated thyroid extracts are available via the Internet. It is important to consider this fact when comparing the present outcomes with the THESIS survey results in other countries.[16,17] Hence, given the limited alternatives available to them, it is logical that Spanish physicians rely almost solely on LT4 as the first line of treatment for hypothyroidism.

Following the international guidelines,[3,4] the specialists rarely considered the non-conventional use of LT4 for non-hypothyroid conditions (such as hypercholesterolemia, obesity, fatigue, obesity or depression). However, several respondents (21.2%) would consider LT4 treatment in euthyroid subjects with simple goitre, even though such treatment is discouraged under current guidelines.[3,4] This result parallels that found in the Italian study,[16] which indicates that this improper practice is deeply rooted in certain sectors. Specific attention deserves the cases of euthyroid seropositive women (with positive antithyroid antibodies) with infertility problems. Almost half of the respondents (48.5%) admitted that this situation warranted thyroid hormone therapy. Interestingly, female specialists, as compared to their male counterparts, were more willing to treat the woman's infertility with LT4 supplements than their male counterparts. Similarly, more experienced physicians (doctors with a high volume of patients) also favoured LT4 supplements in this clinical scenario. This approach has been proposed by recent studies,[18] although there is no clear evidence to substantiate such a claim, and its usefulness remains unsettled.[19]

Cases of persistent hypothyroid symptoms with normal TSH levels, although well known, were rare in the experience of Spanish endocrinologists.[20,21] More than two-thirds stated that such symptoms were reported in fewer than 10% of their hypothyroid patients, and this trend remained unchanged over time. According to respondents, the cause of persistent hypothyroid symptoms is not related to the inability of LT4 to restore normal thyroid physiology. Although there was no evidence to justify their opinion, respondents attributed the persistence of symptoms to psychosocial factors (72%), comorbidities (66%) or unrealistic patient expectations to treatment (65%).[5–7] However, a large proportion of hypothyroid physicians (almost 25%) reckoned to experience fatigue despite treatment, which was in contrast to what specialists stated about the proportion of their patients who were dissatisfied with thyroid hormone supplementation. This may reflect a double standards policy or that there are two different yardsticks applied for the same situation. Clearly, more research is needed.[15]

Despite the lack of experience in treating with combination therapy (due to its unavailability in Spain), many specialists (49%) follow the recommendations of the American and European guidelines,[3,4] and find no reason to recommend LT4 + LT3 therapy as the first-line option for patients with underactive thyroid glands.[22] As in the Italian and Bulgarian THESIS studies.[16,23] and despite the limited availability of combination therapy in Spain, 40% of respondents favoured its use in patients with normal TSH who continued to complain of hypothyroidism-like symptoms. In

Table 4 Opinion of the respondents on various items selected from the survey and classified by gender, years in medical practice, place of employment and frequency of management of patients with hypothyroidism.

Question		Gender			Years in practice			Hospital type			Annual hypothyroid volume		
		Female ($n = 333$)	Male ($n = 169$)	*P*	≤20 ($n = 288$)	>20 ($n = 204$)	*P*	University ($n = 381$)	Other ($n = 124$)	*P*	≤100 ($n = 147$)	>100 ($n = 357$)	*P*
Thyroid hormone may be indicted in biochemically euthyroid females with infertility and thyroid antibodies	*n* (%)	**174 (52.3)**	**69 (40.8)**	**0.018**	**162 (56.3)**	**78 (38.2)**	**<0.001**	185 (48.6)	60 (48.4)	1.000	**56 (38.1)**	**189 (52.9)**	**0.003**
Thyroid hormone is never indicated for biochemically euthyroid subjects	*n* (%)	139 (41.7)	86 (49.1)	0.128	**110 (38.2)**	**107 (52.5)**	**0.002**	170 (44.6)	53 (42.7)	0.755	74 (50.3)	148 (41.5)	0.076
Dietary supplements may be used at the patient' request or as a complementary treatment	*n* (%)	132 (39.6)	54 (32.0)	0.097	**124 (43.1)**	**60 (29.4)**	**0.002**	134 (35.2)	54 (43.5)	0.109	50 (34.0)	137 (38.4)	0.364
Dietary supplements should never be used	*n* (%)	**88 (26.4)**	**67 (39.6)**	**0.003**	**63 (21.9)**	**87 (42.6)**	**<0.001**	121 (31.8)	35 (28.2)	0.503	**62 (42.2)**	**94 (26.3)**	**0.001**

Table 4 (*Continued*)

Question		Gender			Years in practice			Hospital type			Annual hypothyroid volume		
		Female (*n* = 333)	Male (*n* = 169)	*P*	≤20 (*n* = 288)	>20 (*n* = 204)	*P*	University (*n* = 381)	Other (*n* = 124)	*P*	≤100 (*n* = 147)	>100 (*n* = 357)	*P*
The use of LT4 and LT3 combination may be considered in patients with normal TSH who still complain of symptoms	*n* (%)	138 (41.4)	62 (36.7)	0.335	112 (38.9)	84 (41.2)	0.641	148 (38.8)	52 (41.9)	0.597	**43 (29.3)**	**157 (44.0)**	**0.003**
Combined therapy should never be used	*n* (%)	**148 (44.4)**	**96 (56.8)**	**0.011**	135 (46.9)	105 (51.5)		189 (49.6)	58 (46.8)		**86 (58.5)**	**160 (44.8)**	**0.006**
I agree with the opinion that persistent symptoms despite normal TSH are due to psychosocial factors	*n* (%)	238 (71.5)	109 (64.5)	0.125	**217 (75.3)**	**122 (59.8)**	**<0.001**	271 (71.1)	77 (62.1)	0.074	97 (66.0)	251 (70.3)	0.342
I agree with the opinion that persistent symptoms despite normal TSH are due to comorbidities	*n* (%)	213 (64.0)	98 (58.0)	0.207	**189 (65.6)**	**113 (55.4)**	**0.024**	241 (63.6)	71 (57.3)	0.243	84 (57.1)	228 (63.9)	0.160

The data are the number (percentage) of affirmative or favourable responses to each one of the questions indicated. Statistically significant differences (chi-square test) have been highlighted in bold.

Abbreviations TSH, thyrotropin; LT4, levothyroxine; LT3, liothyronine.

Italy, 43% of the respondents expressed support for combination therapy.[16]

Although there are no official guidelines that recommend using iodine in Spain, thanks to the constant efforts of the SEEN, the nutritional status of iodine in the country has improved in recent years, although the problem has not been entirsolved.[24] The lack of an official recommendation is reflected because the participants stated that the first reason to prescribe dietary supplements with iodine or selenium is at the patient's request, while a third considered that dietary supplements should never be prescribed. This situation parallels what is happening in Denmark[17] and reflects the lack of evidence about the clinical benefit of selenium.[25]

Almost a quarter of Spanish practising endocrinologists completed the questionnaire, a relatively high number of participants. There have been very few studies that have aimed to evaluate the real-life practice of specialists. Remarkably, a recent Spanish study conducted by one of the authors of this paper on the attitude of family doctors towards the management of hypothyroidism reveals a proactive attitude in the diagnosis and therapy of hypothyroidism by most respondents.[11] However, the study also noted a tendency of family doctors to perform unnecessary diagnostic tests and an excessive willingness to treat mild subclinical hypothyroidism. This highlights the difference in treatment management between endocrinologists and general practitioners. As stated earlier, the limitations of our analysis are mainly related to the unavailability of combination therapy in Spain and the composition of our sample of respondents that resulted strongly skewed towards young specialists working in university hospitals. For this reason, our results cannot be readily extrapolated to other countries.

Conclusion

The standard of treatment of hypothyroidism in Spain is almost exclusively with LT4 tablets. Availability of other formulations of LT4 or combination therapy for hypothyroidism management remains to be explored, especially in patients with persistent symptoms. Notably, non-evidence-based use of LT4 is widely practised in Spain for euthyroid women with autoimmune thyroiditis and fertility issues.

Financial support

The present investigation has not received any financial support from public sector agencies, commercial sector, or non-profit entities.

Conflicts of interest

PP, LH, EVN and EP are scientific board members of and have received consultancy fees from IBSA Biochemie.

Acknowledgements

We thank all Spanish Endocrine and Nutrition Society members who contributed to the study by answering the questionnaire.

References

1. Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F, Galofré JC. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. J Clin Endocrinol Metab. 2014;99:923–31.
2. Santos Palacios S, Llavero Valero M, Brugos-Larumbe A, Díez JJ, Guillén-Grima F, Galofré JC. Prevalence of thyroid dysfunction in a Large Southern European Population. Analysis of modulatory factors. The APNA study. Clin Endocrinol (Oxf). 2018;89:367–75.
3. Gharib H, Papini E, Valcavi R, Baskin HJ, Crescenzi A, Dottorini ME, et al. AACE/AME Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. Endocr Pract. 2006;12:63–102.
4. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, et al. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association task force on thyroid hormone replacement. Thyroid. 2014;24:1670–751.
5. Thvilum M, Brandt F, Almind D, Christensen K, Brix TH, Hegedüs L. Increased psychiatric morbidity before and after the diagnosis of hypothyroidism: a nationwide register study. Thyroid. 2014;24:802–8.
6. Samuels MH, Kolobova I, Niederhausen M, Janowsky JS, Schuff KG. Effects of altering levothyroxine (L-T4) doses on quality of life, mood, and cognition in L-T4 treated subjects. J Clin Endocrinol Metab. 2018;103:1997–2008.
7. Park SY, Park SE, Jung SW, Jin HS, Park IB, Ahn SV, et al. Free triiodothyronine/free thyroxine ratio rather than thyrotropin is more associated with metabolic parameters in healthy euthyroid adult subjects. Clin Endocrinol (Oxf). 2017;87:87–96.
8. Galofré JC. Trastornos tiroideos y paratiroideos. In: Trastornos del aparato digestivo, metabolismo y sistema endocrino. Madrid: Consejo General de Colegios Oficiales de Farmacéuticos; 2019. p. 18–9. ISBN: 978-84-87089-24-4.
9. Galofré Ferrater JC, Corrales Hernández JJ, Pérez Corral B, Cantón Blanco A, Alonso Pedrol N, Pérez A, et al. Clinical guideline for the diagnosis and treatment of subclinical thyroid dysfunction in pregnancy. Working Group on Subclinical Thyroid Dysfunction of the Spanish Endocrinology Society. Endocrinol Nutr. 2009;56:85–91.
10. Pearce SH, Brabant G, Duntas LH, Monzani F, Peeters RP, Razvi S, et al. 2013 ETA guideline: management of subclinical hypothyroidism. Eur Thyroid J. 2013;2:215–28.
11. Díez JJ, Iglesias P, Gómez-Mateos MA. Management of primary hypothyroidism in adults: an analysis of the results of a survey in 546 primary care physicians. Endocrinol Diabetes Nutr. https://doi.org/10.1016/j.endinu.2021.04.010.
12. Jonklaas J, Bianco AC, Cappola AR, Celi FS, Fliers E, Heuer H, et al. Evidence-based use of levothyroxine/liothyronine combinations in treating hypothyroidism: a consensus document. Thyroid. 2021;31:156–82.
13. Nagy EV, Perros P, Papini E, Katko M, Hegedüs L. New formulations of levothyroxine in the treatment of hypothyroidism: trick or treat? Thyroid. 2021;31:193–201.
14. Mitchell AL, Hegedüs L, Žarković M, Hickey JL, Perros P. Patient satisfaction and quality of life in hypothyroidism: an online survey by the British thyroid foundation. Clin Endocrinol (Oxf). 2021;94:513–20.
15. Perros P, Van Der Feltz-Cornelis C, Papini E, Nagy EV, Weetman AP, Hegedüs L. The enigma of persistent symptoms in hypothyroid patients treated with levothyroxine: a narrative review. Clin Endocrinol (Oxf). doi:10.1111/cen.14473.
16. Negro R, Attanasio R, Nagy EV, Papini E, Perros P, Hegedüs L, et al. Use of thyroid hormones in hypothyroid and euthyroid patients; the 2019 Italian survey. Eur Thyroid J. 2020;9:25–31.

17. Riis KR, Frølich JS, Hegedüs L, Negro R, Attanasio R, Nagy EV, et al. Use of thyroid hormones in hypothyroid and euthyroid patients: a 2020 THESIS questionnaire survey of members of the Danish Endocrine Society. J Endocrinol Invest. 2021:1–10, http://dx.doi.org/10.1007/s40618-021-01555-y.
18. Dhillon-Smith RK, Middleton LJ, Sunner KK, Cheed V, Baker K, Farrell-Carver S, et al. Levothyroxine in women with thyroid peroxidase antibodies before conception. N Engl J Med. 2019;380:1316–25.
19. Plowden TC, Schisterman EF, Sjaarda LA, Zarek SM, Perkins NJ, Silver R, et al. Subclinical hypothyroidism and thyroid autoimmunity are not associated with fecundity. pregnancy loss, or live birth. J Clin Endocrinol Metab. 2016;101:2358–65.
20. Peterson SJ, Cappola AR, Castro MR, Dayan CM, Farwell AP, et al. An online survey of hypothyroid patients demonstrates prominent dissatisfaction. Thyroid. 2018;28:707–21.
21. Taylor PN, Iqbal A, Minassian C, Sayers A, Draman MS, Greenwood R, et al. Falling threshold for treatment of borderline elevated thyrotropin levels-balancing benefits and risks: evidence from a large community-based study. JAMA Intern Med. 2014;174:32–9.
22. Wiersinga WM, Duntas L, Fadeyev V, Nygaard B, Vanderpump MP. 2012 ETA guidelines: the use of L-T4 + L-T3 in the treatment of hypothyroidism. Eur Thyroid J. 2012;1:55–71.
23. Borissova A, Boyanov MA, Attanasio R, Hegedüs L, Nagy E, Negro Roberto, et al. Use of thyroid hormones in hypothyroid and euthyroid patients: a THESIS* questionnaire survey of Bulgarian physicians. *THESIS: Treatment of Hypothyroidism in Europe by Specialists: an International Survey. Endocrinologia. 2020;25:299–309.
24. Vila L, Lucas A, Donnay S, de la Vieja A, Wengrovicz S, Santiago P, et al. Iodine nutrition status in Spain needs for the future. Endocrinol Diabetes Nutr. 2020;67:61–9.
25. Winther KH, Rayman MP, Bonnema SJ, Hegedüs L. Selenium in thyroid disorders – essential knowledge for clinicians. Nat Rev Endocrinol. 2020;16:165–76.