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Artigo Original

Use of Thyroid Hormones in Hypothyroid and Euthyroid Patients: A THESIS Questionnaire Survey of Portuguese Endocrinologists

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A B S T R A C T

Introduction: The standard treatment of hypothyroidism is levothyroxine (LT4), which is available only as tablets in Portugal. This study was part of the European study THESIS (Treatment of Hypothyroidism in Europe by Specialists: an International Survey) and aimed to investigate Portuguese endocrinologists' use of thyroid hormones in hypothyroid and euthyroid patients.
Material and Methods: An e-mail with an invitation to participate in an online survey investigating practices about substitution with thyroid hormones was sent to all physician members of the Portuguese Society of Endocrinology, Diabetes and Metabolism (SPEDM).
Results: Out of 391 eligible SPEDM members, a total of 106 (27.1%) respondents were included in the analysis. The majority (97.2%) used LT4 as the treatment of choice for hypothyroidism. In various conditions that could interfere with LT4 absorption, most respondents (68.0% - 94.3%) preferred tablets and did not expect a significant difference when switching from one type of LT4 formulation to another. Other treatment options for hypothyroidism, such as combination therapy with LT4 and liothyronine (LT3) were rarely used (2.8%). However, the majority of Portuguese physicians (66%) would consider LT4 + LT3 combination in cases of persistent symptoms of hypothyroidism despite biochemical control. Over half of the respondents answered that thyroid hormone therapy is never indicated for euthyroid patients, but 34.9% and 22.6% would consider it for euthyroid infertile women with high anti-thyroid antibody levels and in cases of euthyroid simple growing goiter, respectively.
Discussion and Conclusion: The treatment of choice for hypothyroidism in Portugal is LT4. Combination therapy with LT4 + LT3 would be considered by the majority of respondents for patients with persistent symptoms. Some endocrinologists would offer LT4 to euthyroid infertile woman with high antibody levels and to euthyroid patients with progressively growing simple goiter, contrary to current evidence.

Palavras-chave:
Hipotiroidismo/tratamento farmacológico;
Inquéritos e Questionários;
Levotiroxina;
Sociedades Médicas.

Uso de Hormonas Tiroideias em Doentes Hipotiroideus e Eutiroideus: Aplicação do Questionário THESIS aos Endocrinologistas Portugueses

R E S U M O

Introdução: O tratamento standard do hipotiroidismo consiste em levotiroxina (LT4), disponível apenas sob a forma de comprimidos em Portugal. O presente estudo fez parte do estudo Europeu

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THESIS (*Treatment of Hypothyroidism in Europe by Specialists: an International Survey*) e pretendia investigar a utilização de hormonas tiroideias em doentes em hipotiroidismo e eutiroidismo, pelos endocrinologistas portugueses.

Material e Métodos: Foi enviado um e-mail convite de participação num inquérito online, para investigar a utilização de hormonas tiroideias. Este foi enviado a todos os membros médicos da Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo (SPEDM).

Resultados: Entre os 391 membros elegíveis da SPEDM, foram incluídos na análise 106 (27,1%) respondentes. A maioria (97,2%) utilizava a LT4 como tratamento de escolha para o hipotiroidismo. Em diversas condições que podem interferir com a absorção de LT4, a maioria (68,0% – 94,3%) afirmou preferir a formulação em comprimidos e não esperar diferenças significativas entre as várias formulações. Outras opções terapêuticas, como a combinação de LT4 e triiodotironina (LT3), são raramente utilizadas (2,8%). No entanto, a maioria dos endocrinologistas portugueses (66%), consideraria esta combinação em caso de persistência de sintomas de hipotiroidismo, apesar de controlo bioquímico. Cerca de metade dos respondentes referiram que a terapia hormonal nunca está indicada em doentes eutiroideus. No entanto, 34,9% e 22,6% consideraria em mulheres inférteis em eutiroidismo, com níveis elevados de anticorpos anti-tiroideus, e no bócio simples em crescimento, respetivamente.

Discussão e Conclusão: O tratamento de escolha do hipotiroidismo em Portugal é a LT4. A combinação de LT4 e LT3 foi considerada pela maioria dos respondentes para doentes com persistência de sintomas. Alguns endocrinologistas considerariam a prescrição de LT4 em mulheres inférteis em eutiroidismo com níveis elevados de anticorpos e em doentes eutiroideus com bócio simples em crescimento, contrariamente à evidência atual.

Introduction

Hypothyroidism is a common condition affecting approximately 3% of the European population.[1] A recent study found a similar prevalence in Portugal (4.9%), with a large proportion of undiagnosed patients.[2] Levothyroxine (LT4) is the standard therapy for hypothyroidism, and, in the past decade, different LT4 formulations have become commercially available in Europe (generic or branded, in tablet form, soft-gel capsules or liquid solution).[3]

Soft-gel capsules and liquid solution are the most recent LT4 formulations and were manufactured to overcome some of the bioavailability issues of tablets.[3] Bioavailability of LT4 may be reduced when tablets are administered simultaneously with food and beverages, other types of medication (proton-pump inhibitors, phosphate binders, calcium carbonate, and iron supplements), or in the presence of concomitant gastrointestinal conditions (*Helicobacter pylori* infection, coeliac disease and atrophic gastritis).[3] Preliminary evidence suggests differences in bioavailability in favor of soft-gel capsules and liquid solution both in patients with and without impaired absorption.[3-5] However, new LT4 formulations are more expensive than tablets, and the cost-effectiveness of switching to these formulations remains unsettled.[6] In Portugal, tablets are the only currently available LT4 formulation and there are three brands available. The Portuguese public healthcare system usually funds this medication.

Although Portuguese and international thyroid guidelines uniformly favor LT4 as standard therapy, attitudes diverge regarding combination therapy with LT4 and liothyronine (LT3).[7,8] Interestingly, combination therapy and desiccated thyroid extract (DTE) are gaining popularity in some countries, mostly due to growing demands from patients dissatisfied with LT4 treatment, despite adequate thyroid hormone replacement.[9-13] However, prescribing T3-containing preparations is not without potential risks.[8] Side effects due to possible iatrogenic thyrotoxicosis are a concern, and the available evidence for non-superiority of combination therapy over LT4 does not support this trend.[8] Recently, a Consensus Document on evidence-based use of LT4/LT3 combinations recognized that physiological dosing of LT3 is difficult to achieve using conventional T3 preparations, stating that slow-release T3 preparations are needed to achieve physiological fT3/fT4 levels.[14] Currently, conventional LT3 tablets are not commercially available in Portugal. However, they can be imported from other countries.

This survey was part of the international study THESIS (Treatment of Hypothyroidism in Europe by Specialists: An International Survey). The aim was to investigate the use of thyroid hormones for hypothyroid and euthyroid patients by Portuguese endocrinologists. In Portugal, there is a consensus for the treatment and follow-up of hypothyroidism.[7] Hypothyroid patients are managed in primary and secondary care using the different available LT4 tablets. Most Portuguese physicians work in both private and public health systems.

Material and Methods

A questionnaire was developed to identify attitudes of European endocrinologists regarding substitution with thyroid hormones in hypothyroid and euthyroid patients. The original English survey was translated into Portuguese by a bilingual clinician and checked by a bilingual senior physician (Supplementary Material, Appendix 1). It was adapted to a web-based survey constructed with Google Forms®, an open-access platform. Eight questions about demographic data were followed by twenty-three questions about treatment of hypothyroid and euthyroid patients. Space for comments was available at the end.

An e-mail with an electronic link leading to the voluntary and anonymized questionnaire was sent to all physician members (452 members) of the Portuguese Society of Endocrinology, Diabetes and Metabolism (SPEDM) on 4th February 2021, followed by two reminders in February and March 2021. Survey responses were collected and electronically stored by the survey service, where the data was accessible by password. Repeat submissions from the same Internet Protocol (IP) address were automatically blocked.

Responses from specialties other than endocrinology were excluded. We considered as valid for statistical evaluation only those responses with complete demographic data.

Statistical Analysis

Descriptive statistics were calculated for responses to all questions. The goodness of fit χ^2-test was used to compare frequencies between the categorical 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).

Results

Sample Characteristics

Fig. 1 shows a flowchart of the SPEDM members and the respondents. A total of 106 of 391 eligible members (27.1%) responded, completing all the questions of the survey. Seventeen of the respondents (16.0%) were also members of the European Thyroid Association and two (1.9%) of the American Thyroid Association. The demographic data of the respondents are compiled in Table 1. Eighty-one (76.4%) reported that they treated thyroid patients daily, 24 (22.6%) on a weekly basis, whereas only one (0.9%) rarely managed thyroid patients. Seventy-seven (72.6%) treated more than 100 hypothyroid patients/year, 19 (17.9%) between 51 and 100 annually and 10 (9.4%) only between 10 and 50 annually.

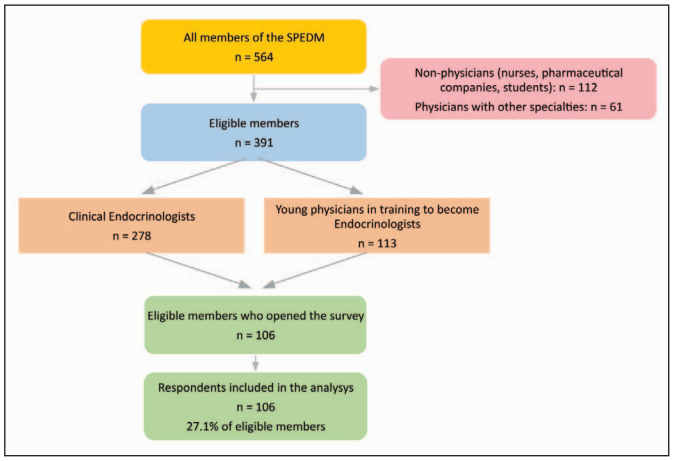

Figure 1. Flowchart illustrating members of the Portuguese Society of Endocrinology, Diabetes and Metabolism and respondents.

Table 1. Characteristics of the 106 respondents.

Gender, n (%)	
Female	74 (69.8)
Male	32 (30.2)
Age in years, n (%)	
20-30	14 (13.2)
31-40	37 (34.9)
41-50	17 (16.0)
>50	38 (34.9)
Years in medical practice, n (%)	
0-10	33 (31.1)
11-20	26 (24.5)
21-30	17 (16.0)
31-40	15 (14.2)
>40	15 (14.2)
Specialisation[a], n (%)	
Endocrinology	106 (100.0)
Paediatric Endocrinology	1 (0.9)
Place of employment[a], n (%)	
Universitary Centre	55 (51.9)
Private clinic	42 (39.6)
Regional Hospital	28 (26.4)
Specialized Medicine	15 (14.2)

[a] The sum of percentages exceeds 100% because some respondents had >1 specialty and were employed in more than 1 place.

Treating Hypothyroid Patients

The great majority of the respondents (103; 97.2%) indicated that the treatment of choice for hypothyroidism is LT4 and the remaining three (2.8%) offered the LT4 + LT3 combination as their first line of therapy (LT4 *vs* LT4 + LT3; $p<0.001$). Regarding prescription in clinical practice, all responders prescribed LT4, while two (1.9%) also prescribed LT3 and one (0.9%) DTE or LT4 + LT3 combination.

Using Different LT4 Formulations

Most of the respondents (76; 71.7%) replied that patients were dispensed the prescribed type of LT4 and 30 (28.3%) reported that to ensure the formulation prescribed was dispensed, they had to provide justification to the regulatory authorities. None believed that they were unable to influence the type of dispensed LT4.

Five survey questions explored the use of different LT4 formulations in specific situations (Table 2). Most Portuguese endocrinologists (up to 52.8%) preferred LT4 tablets to soft-gel capsules or liquid LT4 for the treatment of hypothyroidism, and did not expect any major difference when switching from one type of formulation to another (up to 63.2%). The same attitude applied to situations of interfering drugs, intolerance to various foods, unexplained poor biochemical control, or persistent symptoms despite reasonable biochemical control. One-third of respondents preferred new LT4 formulations in scenarios of expected lower absorption and reduced bioavailability of LT4 tablets (tablets or "no major changes expected" *vs* soft-gel capsules or liquid solution; $p<0.001$).

Monitoring Thyroid Hormone Treatment

After starting LT4 replacement treatment for hypothyroidism, 57 (53.8%) would recheck serum TSH levels in 4-6 weeks and 49 (46.2%) after 8 weeks (4–6 weeks *vs* 8 weeks; $p = 0.437$).

When switching from one formulation or brand to another, 53 (50.0%) would recheck serum TSH levels in 4-6 weeks and 48 (45.3%) after 8 weeks (4–6 weeks *vs* 8 weeks; $p = 0.619$). Four (3.8%) reported to rely only on clinical evaluation and a minority (1; 0.9%) stated that there is no need for TSH monitoring if the dosage is unchanged.

Treating Euthyroid Patients with Thyroid Hormones

The circumstances under which endocrinologists would consider therapy with thyroid hormones in patients without hypothyroidism are shown in Fig. 2. Just over half of the respondents (54; 50.9%) answered that treatment with thyroid hormones is never

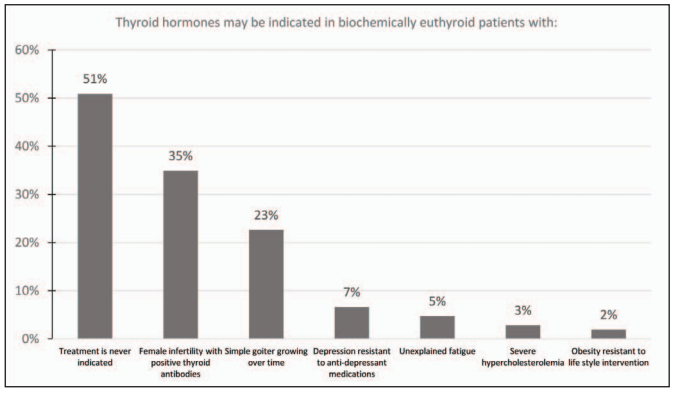

Figure 2. Use of LT4 in euthyroid subjects. Responders were allowed to choose more than one option; hence the total number of responses may be greater than 100%.

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

	Tablets	Soft-gel capsules	Liquid solution	Other brand tablets	"I expect no major changes with the different formulations" n (%)
Interfering drugs may influence the stability of therapy. Which LT4 preparation is in your experience least likely to be subject to variable absorption?	52 (49.1)	10 (9.4)	14 (13.2)	0 (0)	30 (28.3)
Which of the following preparations of LT4 would you prescribe in case of 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	50 (47.2)	13 (12.3)	21 (19.8)	0 (0)	22 (20.8)
Which of the following preparations of LT4 would you prescribe for a patient established on LT4 who has unexplained poor biochemical control of hypothyroidism?	0 (0)	8 (7.5)	11 (10.4)	56 (52.8)	31 (29.2)
Which of the following preparations of LT4 would you prescribe for a patient with poor biochemical control who is unable (due to busy lifestyle) to take LT4 fasted and separate from food/drink?	52 (49.1)	15 (14.2)	18 (17.0)	0 (0)	21 (19.8)
Which of the following preparations of LT4 would you prescribe for a patient established on LT4 tablets who has good biochemical control of hypothyroidism but continues to have symptoms?	0 (0)	2 (1.9)	4 (3.8)	33 (31.1)	67 (63.2)

LT4, levothyroxine

indicated. However, more than a third (37; 34.9%) would consider treatment in euthyroid infertile females with positive thyroid antibodies and approximately a fourth (24; 22.6%) in euthyroid patients with simple goitre growing over time. Other conditions (depression resistant to antidepressant medications, unexplained fatigue, severe hypercholesterolemia and obesity resistant to lifestyle intervention) were rarely considered as indications for treatment (2%-7%).

Combination Treatment with LT4 + LT3

The LT4 + LT3 combination treatment was considered by 70 (66.0%) respondents when symptoms suggestive of hypothyroidism persisted, notwithstanding normal TSH concentration, and by 9 (8.5%), for a short period, in patients recovering from protracted hypothyroidism. Despite this, only three responders actually used LT3 formulations. On the other hand, 27 (25.5%) stated that available evidence does not support combination treatment (LT3 + LT4 *vs* "no evidence"; p <0.001) (Table 3).

Table 3. Use of LT3, LT4 + LT3 combination, desiccated thyroid, selenium and iodine by respondents.

Use of LT3 and desiccated thyroid in clinical practice, n (%)	
LT3	2 (1.9)
LT4 + LT3 combination	1 (0.9)
Desiccated thyroid	1 (0.9)
Consideration of LT4 + LT3 combination use, n (%)	
Never	27 (25.5)
Persistence of hypothyroidism symptoms	70 (66.0)
While recovering from protracted hypothyroidism	9 (8.5)
Consideration of selenium and iodine use, n (%)	
Never	36 (34.0)
If requested by the patient	33 (31.1)
In presence of autoimmune thyroiditis	32 (30.2)
Subclinical hypothyroidism	5 (4.7)

Persistent Symptoms in LT4 Treated Patients

Some patients with hypothyroidism treated with LT4 continue to experience persistent symptoms despite normal serum TSH.[13] Nearly half of the respondents (50; 47.2%) estimated that the frequency of persistent symptoms is less than 5% and approximately a fourth (23; 22%) estimated this figure to be 6%-10%. Nearly a fourth (23; 22%) of the respondents estimated it to be 11%-30% and only a few (3; 2.8%) to be more than 30% (≤ 10% *vs* > 10%, p <0.001). The remaining respondents (7; 6.6%) were not sure. Forty-seven (44%) physicians reported that this trend had not changed over the past five years, whereas 24 (22.6%) reported an increase and 7 (6.6%) a decrease of such cases (no difference vs. more cases; p =0.006). The remaining members (28; 26.4%) were not sure.

Due to the ongoing speculation on the causes of persistent hypothyroid symptoms, Portuguese endocrinologists were asked to comment on eight possible causes of this clinical condition (Fig. 3). Respondents agreed that such persistent symptoms could be mostly due to psychosocial factors (85; 80.2%), comorbidities (70; 66.0%), unrealistic expectations (73; 68.9%), the burden of chronic disease (60; 56.6%) and chronic fatigue syndrome (61; 57.5%). Less than half (50; 47.2%) stated that symptom persistence might be due to inability of LT4 to restore normal physiology.

Supplementation with Selenium and Iodine

Although 36 (34.0%) respondents stated that supplementation with selenium or iodine should never be used, 33 (31.1%)

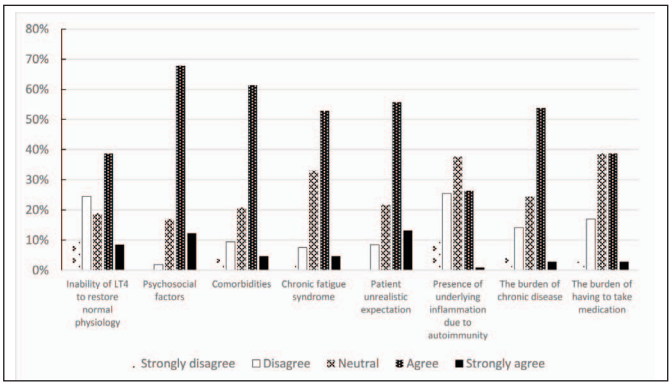

Figure 3. Portuguese endocrinologists' speculation concerning possible factors explaining persistent symptoms of hypothyroidism despite biochemical euthyroidism in patients treated with LT4

answered that it could be used if requested by the patient and 32 (30.2%) that it could be used in patients with co-existing autoimmune thyroiditis. Only five members (4.7%) recommended supplementation in patients with subclinical hypothyroidism (use of selenium and iodine vs. "never use"; p <0.001) (Table 3).

Endocrinologists with Hypothyroidism

Fifteen (14.2%) of the members that completed the survey stated having a diagnosis of hypothyroidism. Of these, 7 (46.7%) reported excessive tiredness. Only one had tried DTE and none had tried combination therapy with LT4 + LT3. Ninety-one respondents (85.8%) claimed not to be diagnosed with hypothyroidism. Of these, only 20 (22.0%) would consider combination therapy with LT4 + LT3 or DTE for themselves in case of hypothyroidism, even if they experienced persistent symptoms despite normalization of serum TSH with LT4 therapy (use of combination therapy or DTE vs. "never use"; p <0.001).

Discussion

Treatment with LT4

This survey confirms that LT4 is the treatment of choice for hypothyroid patients among Portuguese endocrinologists, in accordance with the national guidelines and general consensus.[7] The treatment of choice for hypothyroidism in Portugal, remains LT4 tablets, as there are no other widely available options. Even if different formulations were presently available, less than one-third of SPEDM members would consider prescribing soft-gel capsules or liquid solutions to patients unable to separate LT4 from food intake or interfering drugs or with malabsorption problems, such as gastrointestinal disease, although preliminary evidence seems to supports their use.[3] Portuguese physicians would not consider the use of new LT4 formulations in other situations, such as poor biochemical control on tablets or persistent symptoms despite biochemical control. These results differed from the Italian and Romanian THESIS investigation, where the use of soft-gel capsules and liquid solutions are widely preferred in these clinical conditions.[15-16] The reason for this discrepancy probably rests with the fact that these LT4 formulations are not available in Portugal, while in Italy and Romania they have been available for several years. On the other hand, the results were similar to the Danish and Polish survey, where alternative formulations have been available for a shorter period of time.[17-18] More data on cost-effectiveness is needed to qualify evidence-based use of these new LT4 formulations.

Biochemical follow-up of patients after starting LT4 replacement treatment, or switching from one formulation or brand to another, is performed by more than 95% of Portuguese endocrinologists, who would most frequently recheck TSH within 8 weeks, according to national and international guidelines.[7-19]

Thyroid Hormone Therapy in Euthyroid Patients

In accordance with current guidelines, most respondents agreed that thyroid hormone therapy is never indicated in euthyroid patients. However, more than one in three would consider LT4 treatment in euthyroid infertile women with high levels of thyroid autoantibodies. Infertility has been associated with positive thyroperoxidase antibodies, especially in women with ovulatory dysfunction, but a large prospective study and a recently published randomized clinical trial found no benefit of LT4 treatment in this setting.[20-21]

Additionally, about one in five Portuguese endocrinologists suggested treating a growing goiter with LT4 in euthyroid patients while the evidence demonstrates that the majority of patients with simple goitre do not benefit from this therapy.[22-23] Depression, unexplained fatigue, hypercholesterolemia and obesity were rarely reported as indications for thyroid hormone treatment, in agreement with available evidence.[24-26] With the relevant exception of the treatment with LT4 of euthyroid growing goiter and infertile women, the responses of Portuguese endocrinologists were in accordance with guidelines. Interestingly, similar results were found in other European countries THESIS investigations.[15-17,27]

Combination Therapy with LT4 and LT3

Combination therapy with LT4 + LT3 is discouraged by both American and European guidelines, based on lack of indisputable efficacy.[28-29] However, it might be considered as a short-term trial in hypothyroid patients who have persistent symptoms despite serum TSH values within the reference range.[28] Nearly all respondents considered LT4 the treatment of choice for hypothyroidism, while very few would prescribe LT4 + LT3 combination as a first line therapy. Interestingly, a trial of combination therapy in the presence of persistent symptoms suggestive of hypothyroidism despite normal serum TSH was considered by about 66% of respondents. The fact that only a few actually used it, is probably due to unavailability. Nevertheless, less than half reported that symptom persistence in biochemical euthyroid patients might be due to inability of LT4 to restore normal physiology. These data also differed from the Italian, Romanian, Polish, Spanish and Bulgarian surveys, where combination therapy was considered by 24-40% of endocrinologists in the presence of persistent symptoms.[15,27,30]

Persistent Symptoms in LT4 Treated Patients

Persistent symptoms among biochemically euthyroid patients treated with LT4 are common and the aetiology complex.[13] Psychological factors and comorbidities were pointed out as the main reason for symptoms, in accordance with the known association between autoimmune thyroiditis/thyroid dysfunction and psychiatric disorders and other morbidities.[24,31] Patient satisfaction surveys while on LT4 treatment are quite disappointing, showing even worse results in people with depression.[11]

Supplementation with Iodine and Selenium

The Portuguese guidelines do not support supplementation with iodine or selenium.[7] However, SPEDM members were divided, stating that either dietary supplements should never be used or that they could be used at the request of the patients or in the presence of autoimmune thyroiditis. However, although some evidence suggests that selenium supplementation in chronic autoimmune thyroiditis reduces thyroid autoantibodies, clinical efficacy has not been demonstrated.[32-33] Our findings concur with the Danish and Bulgarian THESIS surveys which also showed that iodine and selenium was recommended by some endocrinologists, regardless of the selenium status of the patients, and without sufficient evidence to support this approach.[17,30]

Treatment of Physicians with Hypothyroidism

The prevalence of hypothyroidism in responding physicians was higher than in the general population, potentially related to an

Appendix 1. Original Survey.

A: ABOUT YOU

A1. Sex
a) Female
b) Male

A2. Age (years) [dropdown menu]
a) 20-30
b) 31-40
c) 41-50
d) >50

A3. Years in medical practice [dropdown menu]
a) 0-10
b) 11-20
c) 21-30
d) 31-40
e) More than 40

A4. Specialty [check all that apply]
a) Endocrinology
b) Internal Medicine
c) Pediatric Endocrinology
d) Nuclear Medicine
e) Surgery
f) Family Medicine
g) Gynecology
h) Other

A5. Member of… [check all that apply]
a) ETA (European Thyroid Association)
b) ATA (American Thyroid Association)
c) LATS (Latin American Thyroid Association)
d) AOTA (Asian and Oceanian Thyroid Association)
e) National Endocrine Societies
f) None of the above

A6. Where do you practice? [check all that apply]
a) University centre
b) Regional hospital
c) Private clinic
d) General Practice
e) Basic researcher

A7. Do you treat thyroid patients on a regular basis (daily or weekly)?
a) Yes, daily
b) Yes, weekly
c) No, I rarely treat thyroid patients

A8. Do you treat patients with hypothyroidism?
a) Yes, from 10 to 50 patients/year
b) Yes, from 51 to 100 patients/year
c) Yes, > 100 patients/year
d) No, I rarely treat hypothyroid patients

B. HYPOTHYROIDISM

B1. Thyroid hormones may be indicated in biochemically euthyroid patients with: [check all that apply]
1) unexplained fatigue
2) obesity resistant to life-style interventions
3) severe hypercholesterolemia, as a complementary treatment
4) depression resistant to anti-depressant medications
5) female infertility with high level of thyroid antibodies
6) simple goiter growing over time
7) no, treatment is never indicated for these patients

B2. Which thyroid hormones available for substitution therapy should be the first choice for the treatment of hypothyroid patients?
1) LT4
2) LT3
3) Desiccated thyroid
4) LT4 and LT3 combination

B3. Which of the following drugs are you prescribing in clinical practice? [check all that apply]
1) LT4
2) LT3
3) Desiccated thyroid
4) LT4 and LT3 combination

B4. How much control do you have over the formulation of LT4 dispensed for your patients? Please choose the option the best applies to your practice
1) most of my patients are dispensed the type of LT4 that I recommend
2) I have control over the type of LT4, but I have to justify it to the regulatory authorities every time I recommend it
3) the type of dispensed thyroxine is mostly chosen by general practitioners
4) for most of my patients I have no control over the type of LT4 that they are dispensed

B5. Interfering drugs may influence the stability of therapy. Which LT4 preparation is in your experience least likely to be subject to variable absorption?
1) tablets
2) soft-gel capsules
3) liquid solution
4) I expect no major changes with different formulations

B6. Which of the following preparations of LT4 would you prescribe in case of 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?
1) tablets
2) soft-gel capsules
3) liquid solution
4) I expect no major changes with the different formulations

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?
1) tablets from another manufacturer
2) soft-gel capsules
3) liquid solution
4) I expect no major changes with the different formulations

B8. Which of the following preparations of LT4 would you prescribe for a patient with poor biochemical control who is unable (due to busy lifestyle) to take LT4 fasted and separate from food/drink?
1) tablets
2) soft-gel capsules
3) liquid solution
4) I expect no major changes with the different formulations

B9. Which of the following preparations of LT4 would you prescribe for a patient established on LT4 tablets who has good biochemical control of hypothyroidism but continues to have symptoms?
1) tablets
2) soft-gel capsules
3) liquid solution
4) I expect no major changes with the different formulations

B10. After the start of LT4 replacement therapy, when would you re-check serum TSH:
1) after 2 weeks
2) after 4 – 6 weeks
3) after 8 weeks
4) no, I mostly rely on clinical evaluation

B11. In case of a switch to a different formulation or change from one manufacturer's LT4 tablet to another, when do you recommend that the serum TSH should be re-checked:
1) after 4 to 6 weeks
2) after 8 weeks
3) on the basis of clinical evaluation
4) no, there is no need of TSH control after preparation changes if the dosage is the same

B12. Dietary supplements (such as selenium or iodine) are proposed for patients with thyroid disease. Do you think that they may be used in addition to thyroid hormone replacement in hypothyroidism?
1) when there is coexisting autoimmune thyroiditis
2) in subclinical hypothyroidism
3) at the patient's request or as a complementary treatment
4) no, dietary supplements should never be used

B13. The use of combined replacement therapy, with administration of both LT4 and LT3, is generally not recommended. Do you think that may be considered?
1) for a short period, in patients recovering from protracted hypothyroidism
2) in patients with normal serum TSH who still complain of symptoms suggestive of hypothyroidism
3) in hypothyroid patients with normal serum TSH who complain of unexplained weight gain
4) due to the low quality of available evidence, combined therapy should never be used.

B14. It has been reported that some patients with hypothyroidism treated with levothyroxine continue to experience persistent symptoms despite normal serum TSH. The following three questions refer to such patients.
In your clinical practice how common is this phenomenon?
1) less than 5% of patients
2) 6%-10%
3) 11%-30%
4) More than 30%
5) Not sure

B15. It has been reported that some patients with hypothyroidism treated with levothyroxine continue to experience persistent symptoms despite normal serum TSH. In your experience what has been the trend over the past 5 years?
1) I am seeing more such cases
2) I am seeing fewer such cases
3) No change
4) Not sure

B16. In most patients treated with levothyroxine who achieve normal serum TSH, persistent symptoms are due to:
1) inability of levothyroxine to restore normal physiology
strongly disagree/disagree/neutral/agree/strongly agree
2) psychosocial factors
strongly disagree/disagree/neutral/agree/strongly agree
3) comorbidities
strongly disagree/disagree/neutral/agree/strongly agree
4) chronic fatigue syndrome
strongly disagree/disagree/neutral/agree/strongly agree
5) patient unrealistic expectation
strongly disagree/disagree/neutral/agree/strongly agree
6) presence of underlying inflammation due to autoimmunity
strongly disagree/disagree/neutral/agree/strongly agree
7) the burden of chronic disease
strongly disagree/disagree/neutral/agree/strongly agree
8) the burden of having to take medication
strongly disagree/disagree/neutral/agree/strongly agree

B17. Using your experience with patients treated with levothyroxine who achieve normal serum TSH, but continue to experience symptoms like fatigue, please rank them from 1-8, where 1 is the most likely and 8 the least likely explanation in your opinion. *[Double-click or drag--and-drop items in the left list to move them to the right - your highest ranking item should be on the top right, moving through to your lowest ranking item].*

	Rank (1-8)
1) the burden of having to take medication	*
2) patient unrealistic expectations	*
3) inability of levothyroxine to restore normal physiology	*
4) psychosocial factors	*
5) presence of underlying inflammation due to autoimmunity	*
6) comorbidities	*
7) chronic fatigue syndrome	*
8) the burden of chronic disease	*

B18. Do you, yourself have a diagnosis of hypothyroidism requiring thyroid hormone treatment?
1. Yes
2. No

B19. *(it will appear only in respondents who answered "yes" to question B18)* **Do you experience excessive tiredness/fatigue?**
1. Yes
2. No

B20. *(it will appear only in respondents who answered "yes" to question B18)* **Have you tried L-T4 and L-T3 combination treatment?**
1. Yes
2. No

B21. *(it will appear only in respondents who answered "yes" to question B18)* **Have you tried desiccated thyroid treatment?**
1. Yes
2. No

B22. *(it will appear only in respondents who answered "yes" to question B20 or B21)* **If you have tried of L-T4 and L-T3 combination treatment or desiccated thyroid, please describe your experience (eg how effective compared with L-T4 monotherapy, whether you continue to take it, side-effects, long-term concerns).**
(Space for free text)

B23. *(it will appear only in respondents who answered "No" to question B18)* **Would you consider L-T4 and L-T3 combination treatment or desiccated thyroid for yourself if you were to develop hypothyroidism?**
1. Yes
2. No

B24. Please add comments (eg why you would or would not choose to take L-T4 and L-T3 combination treatment or desiccated thyroid for yourself)

increased awareness among physicians.[2] Most respondents would not consider combination therapy in case of hypothyroidism, mostly due to lack of evidence. Interestingly, although 66% of the respondents would prescribe combination therapy for their patients in the presence of persistent symptoms, only 22.0% would consider this treatment for themselves.

Strengths and Limitations

The strength of our study is that responses came from clinical endocrinologists who routinely manage a large number of hypothyroid patients. By circulating the questionnaire to all SPEDM members, we obtained 106 responses (27.1% response rate). Most SPEDM members who are clinically active within the thyroid field are organized within the Portuguese Thyroid Study Group, comprising 61 members. The fact that the number of respondents was slightly higher (i.e. 106) indicates that the response rate may be well above 27.1%, taking the relevant target group into account.

The fact that less than one-third of eligible clinicians completed the survey is a limitation of this study and therefore conclusions cannot be easily generalized to the sum of Portuguese endocrinologists. Another limitation is the unavailability of newer LT4 formulations in Portugal and the heterogeneity of access to LT3 throughout the country.

Conclusion

The treatment of choice for hypothyroidism in Portugal is LT4 tablets, even when conditions affecting bioavailability are present. However, some endocrinologists recognize the potential benefits of new LT4 formulations. Moreover, combination therapy with LT4 + LT3 is widely considered for patients treated with LT4 with persistent symptoms and stable TSH within the reference range, although only a few SPEDM members prescribe it in clinical practice due to LT3 unavailability. In a biochemically euthyroid patient, the only scenarios when LT4 was considered by a significant number of physicians were female infertility with positive antibodies or a growing simple goiter. These deviations from guidelines recommendations should be addressed. The Portuguese THESIS study highlights the need for commercialization of LT3 and other LT4 formulations in Portugal.

Contributorship statement / Declaração de contribuição:

FMP: wrote de manuscript.
HS, MM and CF: were responsible for the study in Portugal and reviewed and approved the final manuscript.
RA, LH, EVN, EP ans PP: were responsible for the international study and reviewed and approved the final manuscript.

Responsabilidades Éticas

Conflitos de Interesse: LH, PP, EVN e EP são membros do conselho científico e receberam honorários de consultoria da IBSA Biochimique SA. Todos os outros autores não têm conflito de interesses a declarar. IBSA Biochimique não teve nenhum papel no desenho da pesquisa, análise de dados, apresentação de dados, interpretação de dados ou redação do manuscrito.
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