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# The Use of Thyroid Hormones in Hypothyroid and Euthyroid Patients: A THESIS* Questionnaire Survey of Turkish Physicians

**ABSTRACT**

**Objective:** The incidence of diagnosis of hypothyroidism and the use of thyroid hormones are progressively increasing worldwide. The availability of different thyroid hormone replacement formulations and combinations provides clinicians with various therapeutic choices. The aim of this survey is to document the current approaches of clinicians who manage patients with hypothyroidism in Turkey.

**Methods:** Members of the Society of Endocrinology and Metabolism of Turkey were invited to take part in a web-based survey.

**Results:** A total of 741 members, all clinicians, were invited to respond, and 193 (26%) of them completed the survey. Nearly all (95.9%) participants responded that they treat hypothyroid patients daily. All participants declared that the first treatment of choice for hypothyroidism is levothyroxine. Half of the participants (50.3%), 51.1%, responded that they would not consider using levothyroxine + liothyronine combination in routine clinical practice. Soft and liquid forms of levothyroxine (LT4) were not used as an alternative to tablets although about a quarter of clinicians responded that they would use them if marketed in Turkey. Although 39.4% of respondents estimated that the frequency of patients with persistent symptoms despite achieving euthyroid biochemistry had increased in the last 5 years, two-thirds of them (63.2%) stated that this group comprised less than 10% of all treated hypothyroid patients.

Just under half of the respondents (40.3%) would consider thyroid hormone replacement in biochemically euthyroid patients. The commonest indication (25% of responders) for commencing thyroid hormone therapy in euthyroid patients was female infertility with high level of thyroid peroxidase antibodies. Only 6.8% of participants considered levothyroxine therapy for the treatment of simple goiter.

**Conclusion:** Levothyroxine in tablet form is the treatment of choice for hypothyroidism in Turkey. Despite the absence of robust evidence, half of the clinicians indicated their preference for levothyroxine + liothyronine treatment in specific clinical scenarios. At variance with current guidelines, half of all clinicians would also consider levothyroxine replacement in euthyroid patients, especially thyroid peroxidase antibodies-positive females with infertility.

**Keywords:** Hypothyroidism, thyroid hormones, questionnaire survey

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**THESIS: Treatment of Hypothyroidism in Europe by Specialists: An International Survey*

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## Introduction

The diagnosis of hypothyroidism is gradually increasing worldwide[1] and the number of thyroid hormone prescriptions by different specialists is growing.[2] The clinical presentation of hypothyroidism ranges from lack of symptoms to life-threatening emergencies. In addition, thyroid hormones are sometimes used in the absence of evidence-based indications; this includes but is not limited to biochemically euthyroid patients with complaints such as fatigue, obesity resistant to lifestyle interventions, severe hypercholesterolemia, depression resistant to anti-depressant medications, female infertility with high levels of thyroid antibodies, and simple goiter growing over time.[3-7] Thyroid hormone replacement therapy is usually administered as levothyroxine (LT4) tablets. Of 131 million thyroid hormone prescriptions recorded globally in 2014, 119.5 million (92%) were LT4.[8] In daily practice, discrepancies between targeted and achieved thyroid-stimulating hormone (TSH) levels vary widely during thyroid hormone replacement therapy.[8,9] So, to increase the bioavailability, improve the consistency of absorption of LT4, in various clinical conditions, and increase patients' adherence to treatment, different formulations have been introduced including soft gel capsules and liquid LT4 solutions that were reported to be of value when euthyroidism cannot be achieved due to poor drug compliance, absorption problems, and multiple

drug use in hypothyroid patients.[10-12] Some physicians, influenced by ongoing patient symptoms despite the attainment of biochemical euthyroidism, tend to choose alternative treatment modalities like combined therapy with liothyronine (LT3). The clinical advantages of this approach are not proven while combined therapy carries risks of overtreatment and potentially hazardous fluctuations in serum T3 concentration.[13] So the national guidelines by the Society of Endocrinology and Metabolism of Turkey (SEMT) do not recommend the use of LT4+LT3 combination therapy, as there is insufficient evidence of superiority compared to LT4 therapy alone and recommend that thyroid extract and LT3 should not be used.[14] The consequence of such overtreatment is excess somatic as well as psychiatric morbidity[15,16] and increased mortality, which is related to the time exposed to a serum TSH outside the normal range, especially a low TSH.[17,18] Endemic goiter and iodine deficiency are significant public health problems in Turkey. Erdoğan et al[19] examined both thyroid volumes and urinary iodine concentrations in school-age children and found a 30% prevalence of goiter. National iodization of salt was commenced in 2000 in Turkey with significant improvement in urinary iodine concentration. However, moderate to severe iodine deficiency persists in 27.8% of the Turkish population. Iodine fortification may lead to higher incidence of thyroid autoimmuity[20] and consequent hypothyroidism incidence.

Treatment of Hypothyroidism in Europe by Specialists: an International Survey (THESIS) is a large-scale survey of European physicians who treat patients with hypothyroidism. Here, we report the Turkish contribution to THESIS. The aim of this survey is to document the current approaches of clinicians to the treatment of hypothyroidism in Turkey.

## Material and Methods

The survey was conducted on a web-based system (Google Form interface). It commenced on August 15, 2020, and ended on October 30, 2020, preceded by 2 reminders. The English version of the questionnaire was translated into Turkish by a bilingual clinician

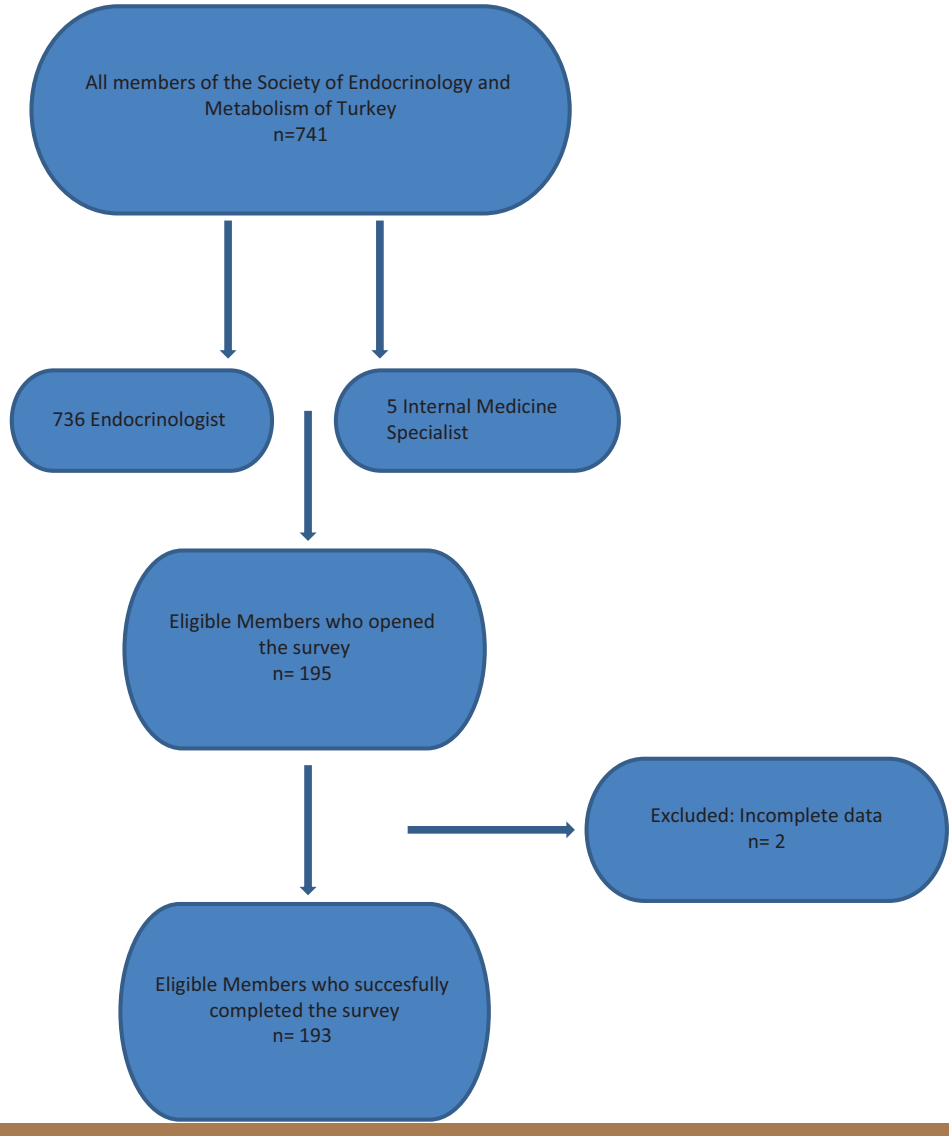


Figure 1. Flowchart illustrating invited members of the Society of Endocrinology and Metabolism of Turkey for "Questionnaire Survey on Current Use of Levothyroxine in Turkey."

and checked by 2 bilingual senior physicians. The questionnaire included 8 questions focusing on defining the clinical background and the working setting of responders and 17 questions focusing on their approaches to the treatment of hypothyroidism. The survey link was sent via e-mail to all members of SEMT (n = 741). A total of 193 members of SEMT completed all questions. Two members who answered the questionnaire incompletely were excluded from the study (Figure 1). Eligibility criteria were defined as being a member of SEMT and filling out the questionnaire completely. Anonymized responses were collected electronically. The storage area containing the answers could only be entered with a password. Replies from the same e-mail address were automatically blocked.

### *Survey and Data Management*

Respondents agreed to fill out the survey voluntarily, were aware that they could at any point leave the survey and did not receive any incentives. Personally identifiable data were not collected. The national leads and Steering Committee were responsible for data integrity and safekeeping for locally collected and aggregated data, respectively. An institutional board review was not necessary as the survey was anonymous.

### *Statistical Analysis*

Summary statistics were prepared for the answers to each question. Descriptive data were calculated for the questions. Data were analyzed using Statistical Package for the Social Sciences Statistics version 27 software (IBM Corp.; Armonk, NY, USA). Two-sided *P* values of <.05 were considered statistically significant. The chi-square test was used to compare frequencies between the categorical variables. Pearson's $\chi^2$-test was used to test for independent demographic data, and a logistic regression analysis was done if any variable was dependent.

## Results

All respondents were SEMT members (n = 193) and 20 of them (10%) were also members of the European Thyroid Association (ETA). Descriptive information of the participants who answered all questions in the questionnaire is shown in Table 1. Of the respondents, 62.7% (121/193) treated more than 500, 29.5% (57/193) between 101 and 500, and 7.8% (15/193) less than 100 hypothyroid patients per year. Of the participants, 95.9% (185/193) encountered hypothyroid patients daily in their practice, while 4.1% (8/193) treated hypothyroid patients on average once weekly.

**Table 1. Characteristics of the 193 Survey Participants**

| | |
|---|---|
| Gender, n (%) | |
| Male | 86 (44.5) |
| Female | 107 (55.5) |
| Years in medical practice, n (%) | |
| ≤10 | 33 (17.0) |
| 11-20 | 69 (35.7) |
| 21-40 | 81 (42.0) |
| >40 | 10 (5.3) |
| Specialization, n (%) | |
| Endocrinology | 188 (97.4) |
| Internal medicine | 5 (2.6) |
| Place of employment[1], n (%) | |
| University hospital | 119 (58.0) |
| State hospital | 41 (20.0) |
| Private clinic | 41 (20.0) |
| Other | 3 (1.0) |

[1]This sum exceeds 193 participants since some responders worked in more than 1 institution.

**Table 2. Participant Responses Regarding Indications for Thyroid Hormones Treatment in Biochemically Euthyroid Patients**

| Variables | Respondents[1] | % |
|---|---|---|
| Unexplained fatigue | 8/236 | 3.4 |
| Obesity resistant to life style interventions | 3/236 | 1.3 |
| Severe hypercholesterolemia, as a complementary treatment | 2/236 | 0.8 |
| Depression resistant to antidepressant medications | 7/236 | 3.0 |
| Female infertility with high levels of thyroid antibodies | 59/236 | 25.0 |
| Simple goiter growing over time | 16/236 | 6.8 |
| Treatment is never indicated | 141/236 | 59.7 |
| Total answer count | 236 | 100.0 |

[1]Respondents were allowed to select more than 1 answers.

All participants declared that the initial treatment of choice for hypothyroidism was LT4. The distribution of the answers to the question "In which clinical conditions thyroid hormone replacement can be used in biochemically euthyroid patients?" is shown in Table 2. More than half of the participants (59.7%) responded that there is no indication for any thyroid treatment in any of these conditions. However, more than one-third of the participants (40.3%) thought that LT4 treatment can be used in biochemically euthyroid patients. The most common reason to start thyroid hormone therapy in euthyroid patients was female infertility associated with a high level of thyroid antibodies (25%). Simple goiter growing over time, unexplained fatigue, depression resistant to anti-depressant medications, obesity resistant to lifestyle interventions, and severe hypercholesterolemia were rare indications for LT4 treatment in euthyroid patients.

Half of the participants (50.3%), 51.1%, did not consider the use of LT4 + LT3 combination due to lack of high-quality evidence (Figure 2).

Two different brands of LT4 in different amounts, 1 brand of 25 mg LT3 and 1 brand of 50/12.5 mg LT4 + LT3 fixed combination in a single tablet, are available on the Turkish market. The distribution of the answers to the question "which forms would be preferred in different clinical situations, if all formulations existed on the market" is shown in Figure 3.

Among the answers given to the question about which LT4 preparation showed the least variation in absorption, 39.9% of the participants chose tablets. About 30% of respondents did not expect any difference in absorption between formulations.

More than half of the participants (54.9%) would consider using selenium or iodine supplementation in case of selenium or iodine deficiency diagnosed by serum selenium or 24-hour urine iodine measurements. 22.3% of the participants stated that they never recommend iodine or selenium supplementation. The distribution of answers given to the question "Do you think these supplements can be used in addition to thyroid hormone replacement in hypothyroidism?" is shown in Figure 4. 54.9% (106/193) of the participants stated that they would use these supplements if they could

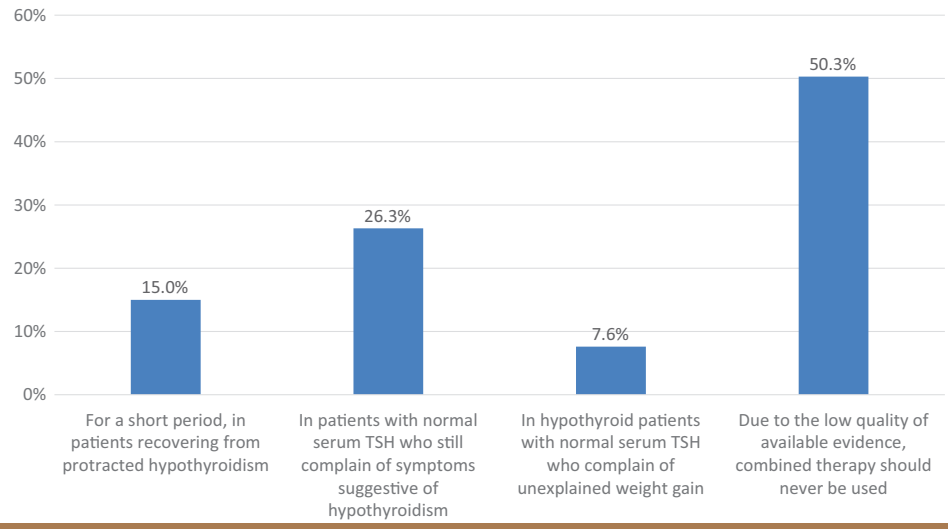


Figure 2. Participant responses regarding possible indications for combined LT4+ LT3 treatment. Few respondents gave more than 1 answer. LT4, levothyroxine; LT3, liothyronine.

document iodine or selenium deficiency in addition to thyroid hormone replacement therapy.

After the start of LT4 replacement therapy, 132 of the participants (68.4%) measured TSH after 4-6 weeks, while 61 (31.6%) after 8 weeks. When switching to a different formulation or manufacturer of LT4, 103 (53.6%) of the participants would measure TSH after 4-6 weeks, while 78 (40.4%) would do so after 8 weeks.

Participants considered that psychosocial factors, chronic fatigue syndrome, and comorbidities were the most common causes of persistent symptoms in biochemically euthyroid patients as shown in Table 3.

According to the experience of the majority of participants (63.2%), 10% of patients had persistent symptoms despite being biochemically euthyroid on thyroid hormone replacement; 39.4% thought that the prevalence of such patients had increased over the last 5 years, while 33% thought that there was no change (Table 4).

Using multivariate analysis, it was shown that responses to this question were unrelated to age, sex, years in medical practice, or place of employment of responders. In total, 32.1% (62/193) of the respondents chose to use LT4 + LT3 combination for patients who attained euthyroidism but complained of persisting symptoms.

## Discussion

The healthcare system in Turkey consists of family medicine (general practitioners), public hospitals, university hospitals, private hospitals, and private clinics. The family medicine system is implemented throughout the country. Although each person is linked to a general

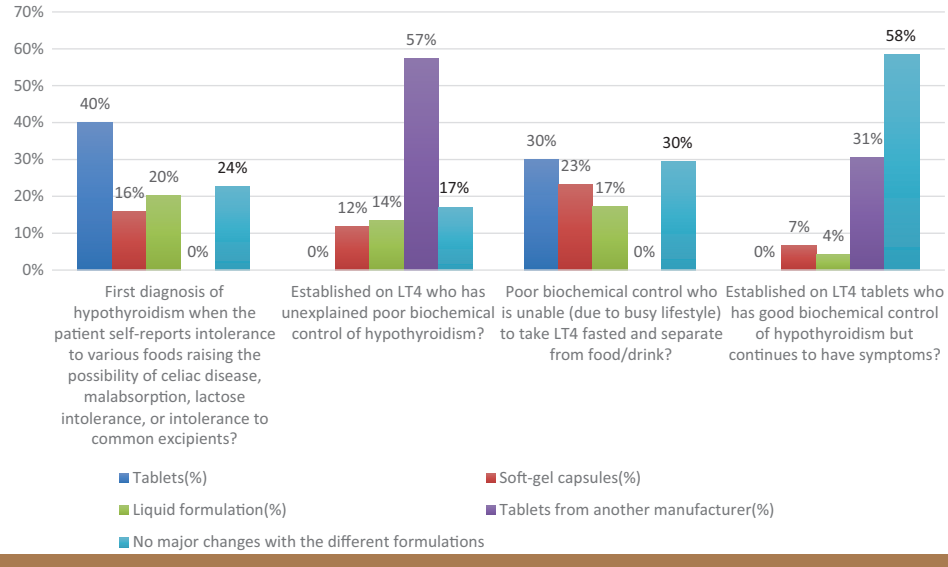


Figure 3. Preferences of LT4 formulations by respondents (who were asked to record their choice if they were all available on the market) in different clinical scenarios. The stem of the question was " Which of the following preparations of LT4 would you prescribe in case of... ." LT4, levothyroxine.

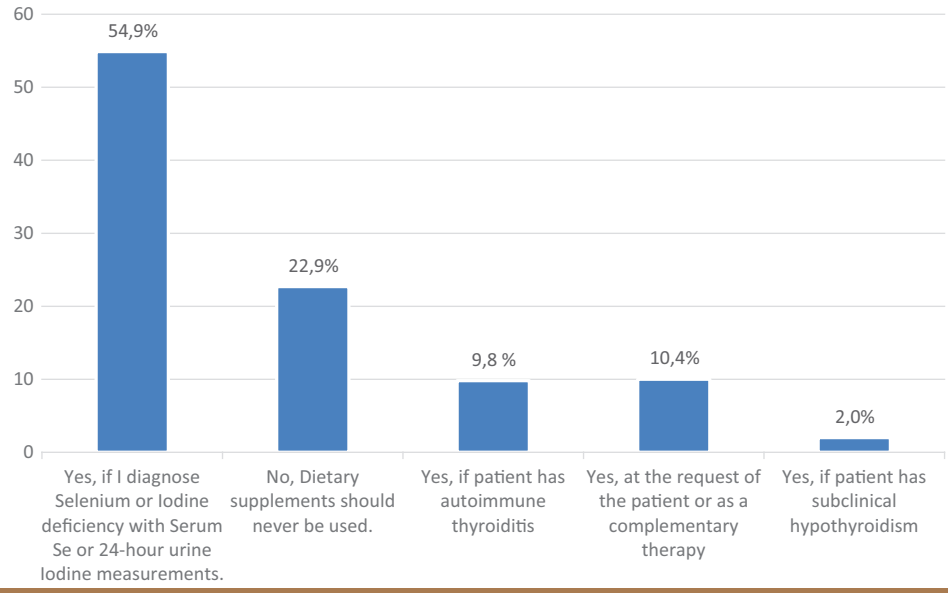


Figure 4. The distribution of answers given to the question "Do you think these supplements can be used in addition to thyroid hormone replacement in hypothyroidism."

practitioner, patients can access a higher healthcare tier without any restrictions.[21] Hypothyroidism is being treated mainly by endocrinologists, internal medicine specialists, and to a lesser extent by general surgeons mostly in secondary or tertiary referral centers.

This survey has shown that, in accordance with the guidelines recommendations, LT4 is the first choice by physicians dealing with a large volume of hypothyroid patients for the treatment of hypothyroidism in Turkey. Half of the Turkish participants never use LT4+LT3 combination therapy, while the remainder thinks that it could be used in specific circumstances, namely, for a short period in patients recovering from protracted hypothyroidism, in patients with normal serum TSH who still have symptoms of hypothyroidism, and in hypothyroid patients with normal serum TSH who suffer from unexplained weight gain. Notably, there is a wide variation throughout Europe for the use of LT4+LT3 for these conditions. In studies conducted in Denmark,[6] Italy,[5] Bulgaria,[4] Romania,[3] Spain[22,] and Poland[7,] the rates of using LT4+LT3 combination therapy in patients with persistent symptoms achieving a normal TSH under medication are 71%, 40%, 6%, 35.9%, 2.6%, and 30.2%, respectively. These approaches appear inappropriate because, although some studies suggest that combination therapy may be beneficial, high-quality evidence confirming its superiority is lacking.[23,24] Moreover the ETA and the American Thyroid Association (ATA) guidelines do

**Table 4. Participants' Views About the Numbers of Patients with Persistent Symptoms Despite Being Euthyroid**

| Determinants | Responses | Number (%) |
|---|---|---|
| Frequency of persistent symptoms in patients with normal TSH | <5% | 70 (36.3) |
| | 6%-10% | 52 (26.9) |
| | 11%-30% | 37 (19.2) |
| | More than 30% | 19 (9.8) |
| | Not sure | 15 (7.8) |
| Trend in last 5 years | I am seeing more cases | 76 (39.4) |
| | I am seeing fewer such cases | 21 (10.9) |
| | No change | 64 (33.1) |
| | Not sure | 32 (16.6) |

TSH, thyroid-stimulating hormone.

**Table 3. Participants' Views About the Cause of Persistent Symptoms in Biochemically Euthyroid Patients**

| Etiology/Answer | Strongly Disagree (%) | Disagree (%) | Neutral (%) | Agree (%) | Strongly Agree (%) |
|---|---|---|---|---|---|
| Inability of LT4 to restorenormal physiology | 20 (10.4) | 44 (22.8) | 36 (18.7) | 74 (38.3) | 19 (9.8) |
| Psychosocial factors | 8 (4.1) | 13 (6.7) | 12 (6.2) | 117 (60.6) | 43 (22.3) |
| Comorbidities | 8 (4.1) | 15 (7.8) | 20 (10.4) | 119 (61.7) | 31 (16.1) |
| Chronic fatigue syndrome | 9 (4.7) | 9 (4.7) | 23 (11.9) | 117 (60.6) | 35 (18.1) |
| Unrealistic patient's expectations | 9 (4.7) | 25 (13) | 25 (13) | 92 (47.7) | 42 (21.8) |
| Underlying inflammation due to autoimmunity | 9 (4.7) | 39 (20.2) | 52 (26.9 | 81 (42) | 12 (6.2) |
| Burden of chronic disease | 8 (4.1) | 36 (18.7) | 58 (30.1) | 80 (41.5) | 11 (5.7) |
| Burden of having to take medication | 10 (5.2) | 29 (15) | 55 (28.5) | 84 (43.5) | 15 (7.8) |

LT4, levothyroxine.

not recommend the use of combination therapy in the routine management of patients with hypothyroidism.[25,26] Possible reason might be the unavailability of other formulations of LT4 in the market.

Studies suggest that the liquid form of LT4 is effective when taken with breakfast or with that may interfere with the absorption of LT4 tablets (proton-pump inhibitors, aluminum-containing antacids, calcium carbonate, ferrous sulfate, sucralfate, raloxifene, bile acid sequestrants, and phosphate binders).[10] However, the strength of evidence is weak, and randomized prospective trials are necessary to determine the role of liquid LT4 and soft gel, especially given their higher cost.[11] These may be reasons why Turkish physicians would prefer other LT4 formulations to tablet form in patients who did not achieve euthyroidism due to different scenarios, if those formulations were available on the market. In addition to the unavailablity of other formulations on the market, other reasons might be decisive for 60% of Turkish clinicians in preferring a different brand when patients' symptoms persisted despite adequate biochemical control. Two highly bioequivalent tablet form brands of LT4 are available in Turkey. However, although it is not proven by a well-designed prospective study, anecdotal evidence suggests that switching one tablet brand to another may be beneficial in achieving euthyroidism or in resolving the ongoing symptoms of biochemically euthyroid patients.

In our survey, clinicians stated that they would re-evaluate TSH levels 8 weeks after changing the brand. This approach is consistent with the recommendation of the ATA stating that patients should remain on the same LT4 product for as long as possible, and in case of change in the product, thyroid function should be rechecked.[26]

Only 41.3% of the participants considered introducing thyroid hormone replacement in euthyroid patients scenarios as outlined in Table 2, compared to 60% in Bulgaria,[4] 47.6% in Italy,[5] 51.3% in Denmark,[6] 55.8% in Spain[22,] and 52% in Romania.[3]

According to our survey data, physicians rarely prescribed thyroid hormones for unexplained fatigue, lifestyle-resistant obesity, presence of severe hypercholesterolemia despite treatment, or antid epressant-resistant depression. This approach is consistent with the available evidence.[25,26] Using multivariate analysis, age, sex, years in medical practice, or place of employment of responders were not found to correlate to participants' answers for thyroid hormone usage in euthyroid patients with persistent symptoms. However, 1 in 4 respondents indicated that LT4 therapy may be used in female infertility associated with the presence of high thyroid autoantibody levels even if the patient is euthyroid. Although a meta-analysis investigating 47 045 pregnant women showed an association between TPOAb positivity and preterm labor (odds ratio, 1.36; $P < .001$),[27] large-scale randomized clinical studies demonstrated the use of LT4 in infertile women with TSH < 2.5 mIU/L and positive thyroid autoantibodies without any effects on infertility. Moreover, in another study, LT4 treatment was not found to be beneficial for live birth rates in euthyroid pregnant women with TPOAb positivity.[28] A recent study showed that LT4 replacement in euthyroid antibody-positive patients who underwent in vitro fertilization and embryo transfer achieved no benefit in live births and miscarriage risk.[29] The benefit is not clear in the literature.[30] This discrepancy between clinical evidence and practice is concerning and requires further exploration.

Until a couple of decades ago, TSH suppression therapy was widely used to shrink the volume of nodular goiter. Subsequent evidence has proven this as ineffective and potentially harmful and that most patients are ineligible.[31-34] In our survey, in accordance with current recommendation, only 6.8% of participants considered LT4 therapy for these purposes.

Almost half of the participants (54.9%, 106/193) stated that they would use iodine or selenium supplements in case of documented deficiency during replacement therapy for hypothyroidism. The benefit of selenium supplementation adding to thyroid replacement therapy is not clear in the literature.[35] Turkey is an iodine-deficient area and salt has been fortified with iodine for many decades. Although recent studies have clearly demonstrated that thyroid antibody positivity after iodization is transient and not clinically significant, participants would not choose iodine supplementation unless iodine deficiency was documented.[19,36-39]

The strength of this study is that it was conducted among professionals most of whom see many hypothyroid patients, across all Turkish regions. The limitations include the relatively low response rate of 33%.

In conclusion, LT4 in tablet form is the treatment of choice for the treatment of hypothyroidism in Turkey. Half of the clinicians would consider LT4 + LT3 combination in specific clinical scenarios despite the absence of clear evidence. At variance with current guidelines, half of all clinicians would also consider LT4 replacement in euthyroid patients, especially TPOAb-positive females with infertility.

**Ethics Committee Approval:** An institutional board review was not necessary as the survey was anonymous.

**Informed Consent:** Respondents agreed to fill out the survey voluntarily, were aware that they could at any point leave the survey and did not receive any incentives. Personally identifiable data were not collected. The national leads and Steering Committee were responsible for data integrity and safekeeping for locally collected and aggregated data, respectively.

**Peer-review:** Externally peer-reviewed.

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