



Use of thyroid hormones in hypothyroid and euthyroid patients: a THESIS* questionnaire survey of Polish physicians

*THESIS: Treatment of hypothyroidism in Europe by specialists: an international survey

Tomasz Bednarczuk¹, Roberto Attanasio², Laszlo Hegedüs³, Endre V. Nagy⁴, Roberto Negro⁵, Enrico Papini⁶, Petros Perros⁷, Marek Ruchala⁸

¹Department of Internal Medicine and Endocrinology, Medical University of Warsaw, Warsaw, Poland

²Endocrinology Service, IRCCS Orthopaedic Institute Galeazzi, Milan, Italy

³Department of Endocrinology and Metabolism, Odense University Hospital, University of Southern Denmark, Odense, Denmark

⁴Division of Endocrinology, Department of Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

⁵Division of Endocrinology, V. Fazzi Hospital, Lecce, Italy

⁶Department of Endocrinology and Metabolism, Ospedale Regina Apostolorum, Rome, Italy

⁷Department of Endocrinology, Royal Victoria Infirmary, Newcastle upon Tyne, United Kingdom

⁸Department of Endocrinology, Metabolism and Internal Medicine, Poznan University of Medical Sciences, Poznan, Poland

Abstract

Introduction: Over the past several years new evidence on the management of hypothyroidism has emerged, which has influenced recommendations from professional bodies. The presentation of hypothyroid patients has also changed, and new cases are increasingly diagnosed by indiscriminate screening, often identifying cases with minor biochemical disturbances. Little is known about the physician responses and attitudes to this changing landscape. THESIS (Treatment of Hypothyroidism in Europe by Specialists: an International Survey) is a large-scale survey of European physicians who treat patients with hypothyroidism. Here we document current practices of Polish physicians relating to the use of thyroid hormones in hypothyroid and euthyroid patients.

Material and methods: Members of the Polish Society of Endocrinology were invited to participate in the web-based THESIS survey.

Results: In total 423 (54.6% of the 774 invited) physicians completed the survey. The majority of respondents (74.2%) would prescribe thyroid hormones for euthyroid patients for certain indications, such as female infertility with elevated thyroid antibodies (63.4%), simple goitre (40.9%), unexplained fatigue (12.1%), obesity (9.7%), hypercholesterolaemia (9.0%), and depression (9.2%). Nearly all physicians (96.0%) declared that the treatment of choice for hypothyroidism is levothyroxine (LT4). However, around one-third (30.3%) were also using LT4 and liothyronine (LT3) combination treatment; LT3 alone was rarely prescribed (1.7%), and none prescribed desiccated thyroid extract. The majority of respondents preferred LT4 tablets. Among alternative formulations, liquid LT4 was most commonly recommended for patients unable to take LT4 in the fasting state (26.0%) and patients with malabsorption (19.9%). Respondents considered prescribing dietary supplements (such as selenium and iodine) in hypothyroid patients with coexisting autoimmune thyroiditis (29.6%) or at the patients' request (32.2%). LT4 + LT3 combination therapy was used by 32.2% when symptoms persisted notwithstanding normal serum TSH concentration. Psychosocial factors, comorbidities, and the burden of chronic disease were considered as the most likely causes of persistent symptoms.

Conclusions: Apart from clinical practice recommendations, other factors influence the thyroid hormone therapy patterns. Moreover, certain areas of clinical practice were identified (the use of thyroid hormones in euthyroid subjects and the use of dietary supplements), which are not in accordance with the current evidence. (*Endokrynol Pol* 2021; 72 (4): 357–365)

Key words: survey; hypothyroidism; thyroid hormones; levothyroxine; liothyronine; desiccated thyroid extracts; iodine; selenium

Introduction

Primary hypothyroidism is one of the most common endocrine disorders and typically requires lifelong treatment with thyroid hormone [1]. Levothyroxine (LT4) is the mainstay of replacement therapy, and the World Health Organization considers LT4

tablets as an essential medicine for basic health care (<https://list.essentialmeds.org/>). Although the management of hypothyroidism with LT4 tablets is generally described as “simple, cheap, effective, and safe”, physicians may encounter several difficulties during treatment [2–5]. LT4 is classified as having a narrow therapeutic index, indicating that small differences in



Tomasz Bednarczuk, Department of Internal Medicine and Endocrinology, Medical University of Warsaw, ul. Banacha 1a, 02-097 Warsaw, Poland, tel: (+48) 22 599 2975, fax: (+48) 22 599 1975; e-mail: tbednarczuk@wum.edu.pl

Marek Ruchala, Department of Endocrinology, Metabolism, and Internal Medicine, Poznan University of Medical Sciences, ul. Przybyszewskiego 49, 60-355 Poznań, Poland, tel: (+48) 61 869 1330, fax: +48 61 869 16 82; e-mail: mruchala@ump.edu.pl

dose or blood concentrations may lead to therapeutic failure (under- or overtreatment) [6]. Malabsorption syndromes, and various drugs and foods may affect T4 absorption, influencing therapy [7–9]. While most patients report improved well-being during LT4 therapy, some patients remain inadequately treated with elevated TSH levels and/or persistent symptoms [10]. Moreover, online surveys of hypothyroid patients on LT4 tablets indicate that impaired quality of life and dissatisfaction with LT4 therapy is common. [11, 12].

Other options of thyroid hormone replacement therapy include the following: different LT4 formulations (soft-gel capsules or liquid solution), liothyronine (LT3), a combination of LT4 and LT3, and desiccated thyroid extracts (DTE). However, the availability of alternative forms of thyroid hormone replacement therapy varies between countries [13]. Various brands and formulations of thyroid hormone are available to prescribers in Poland (Tab. 1). Only LT4 tablets produced by two different manufacturers are reimbursed by the National Health Fund. LT4 as a liquid solution has been commercially available since the last quarter of 2020, whereas LT4 soft-gel capsules, LT3, and DTE are unavailable.

Different LT4 preparations are prescribed with variable frequency by endocrinologists and practitioners [14]. Furthermore, national differences in the prescription of LT4 and a continuing upward trend across time, suggestive of lowering thresholds employed by physicians in initiating treatment, have been noted [15–17]. Switching from one LT4 preparation to another appears to incur a significant economic cost [18–20]. Understanding the prescribing preferences of physicians is important because it has an impact on

health care costs and the patient experience. A recent survey focusing on the controversial topic of use of combination LT4 and LT3 treatment in hypothyroidism revealed that the physician's choice of treatment was powerfully influenced by ongoing patient symptoms and characteristics independently of biochemical control of hypothyroidism [21]. This is a concerning trend given the lack of evidence for superiority of T3 treatment and the risks of subclinical hyperthyroidism. LT4-only preparations have the advantage (over T3) of restoring physiological levels of thyroid hormones without the potentially hazardous fluctuations in serum T3 concentration. However, physician prescribing choices among different thyroid hormone preparations has not been studied in the context of persistent patient symptoms. Currently, physicians' prescribing choices between different thyroid hormone preparations are being studied in various European countries using the THESIS questionnaire (Treatment of Hypothyroidism in Europe by Specialists: an International Survey) [22–24], of which the present study was a part. The aim was to identify clinical practice attitudes of Polish physicians relating to treatment of hypothyroidism with a focus on available formulations of LT4.

Material and methods

The online questionnaire platform Lime-Survey (<https://www.limesurvey.org/>), which provides various question templates, was used. The THESIS questionnaire consisted of 32 questions (8 concerning demographic data and 22 concerning thyroid hormone use). The English version of the questionnaire was translated into Polish by a bilingual clinician and checked by two bilingual senior physicians. Active members of the Polish Society of Endocrinology, whose e-mails were available on the website <http://www.en.ptendo.org.pl/>, were invited to participate (n = 774), without a previous pre-

Table 1. Various brands and formulations of thyroid hormones available to prescribers in Poland at the time of the survey

Thyroid hormone	Pharmaceutical formulation	Name of the product*	MAH	Strength [μ g]	Reimbursement**
LT4	Tablet	Eltroxin®	Aspen Pharma Trading Ltd	50 and 100	No
LT4	Tablet	Euthyrox N®	Merck Sp. z o.o.	25, 50, 75, 88, 100, 112, 125, 137, 150, 175, and 200	Yes
LT4	Tablet	Letrox®	Berlin-Chemie AG	50, 75, 100, 125, and 150	Yes
LT4	Oral solution	Tirosint Sol®***	IBSA Farmaceutici Italia S.r.L.	13, 25, 50, 75, 88, 100, 112, 125, 137, 150, 175, and 200	No
LT4 and LT3	Tablet	Novothyral® Novothyral 75®	Merck Sp. z o.o.	100 μ g LT4 + 20 μ g LT3/tablet; 75 μ g LT4 + 15 μ g LT3/tablet	No

Based on summary of product characteristics. LT4 — levothyroxine; LT3 — liothyronine; MAH — Marketing Authorisation Holder. *In alphabetical order.

Reimbursement by the National Health Fund (*Narodowy Fundusz Zdrowia* — NFZ). *Tirosint Sol: date of first authorization — 21 January 2020, introduction on the market - the last quarter of 2020

selection. All received an initial e-mail, including an electronic link to the questionnaire, followed by 4 reminders at weekly intervals between September 1st and 4th October 2020. Anonymized survey responses, accessible only via passwords, were collected and stored electronically by the survey service, which automatically blocked repeat submissions from the same IP address.

Statistical analysis

Questionnaires were considered valid for statistical evaluation only when complete demographic data were provided by respondents. Descriptive statistics were prepared for responses to each question and presented as numbers (percentages). Pearson's χ^2 test or Fisher's exact test were used to compare frequencies (percentages) between categorical variables. Two-sided p-values < 0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 23 software (SPSS, Chicago, IL, USA).

Results

Data about the survey respondents

In total, 459 members of the Polish Society of Endocrinology (59.5% of the 774 invited) participated in the survey, 423 of whom (92.2%, 423 of 459) completed all demographic data (Tab. 2). The majority were specialists in endocrinology (86.8%), had more than 10 years of clinical practice (82.8%), and treated thyroid patients on a daily basis (88%). The vast majority (79%) managed more than 100 hypothyroid patients per year, while 1.7% rarely treated hypothyroid patients.

Treating patients with thyroid hormones

Around three-quarters of respondents (314 of 423, 74.2%) would prescribe thyroid hormones for patients with biochemically normal thyroid function for certain indications (Fig. 1). The two most frequently chosen indications were female infertility associated with elevated thyroid antibodies (268 of 423, 63.4%) and simple goitre growing over time (173 of 423, 40.9%). Other rarer indications included the following unexplained fatigue (12.1%), obesity resistant to lifestyle intervention (9.7%), severe hypercholesterolaemia (9.0%) as a complementary treatment, and depression resistant to anti-depressant medications (9.2%).

Nearly all physicians (406 of 423, 96.0%) answered that the treatment of choice for hypothyroidism is LT4, with only one (0.2%) choosing LT3 (Tab. 3). Consequently, nearly all respondents were prescribing LT4 in clinical practise. However, around one-third were also using LT4 and LT3 combination treatment (128 of 423, 30.3%); LT3 alone was rarely prescribed (1.7%), and nobody prescribed DTE. Subgroup analysis revealed that physicians older than 40 years, those with more than 10 years medical practice, and those treating more than 100 hypothyroid patients per year more often prescribed LT4 + LT3 combination therapy

Table 2. Characteristics of analysed respondents (n = 423)

Characteristic	n (%)
Gender	
Female	290 (68.6)
Male	133 (31.4)
Age	
20–30	29 (6.9)
31–40	97 (22.9)
41–50	119 (28.1)
51–60	111 (26.2)
61–70	60 (14.2)
70+	7 (1.7)
Years in medical practice	
0–10	93 (22.0)
11–20	113 (26.7)
21–30	109 (25.8)
31–40	85 (20.1)
40+	23 (5.4)
Speciality*	
Endocrinology	367 (86.8)
Internal Medicine	282 (66.7)
Paediatric Endocrinology	20 (4.7)
Nuclear Medicine	31 (7.3)
Gynaecology	15 (3.5)
Other**	48 (11.3)
Member*	
Polish Society of Endocrinology	406 (96)***
European Thyroid Association	45 (10.6)
American Thyroid Association	2 (0.5)
None of the above	17 (4)****
Place of employment*	
University centre	194 (45.7)
Regional hospital	55 (13)
Private clinic	255 (60.1)
General practice	36 (8.5)
Basic researcher	40 (9.5)*****
Specialist practice	234 (55.3)
Treatment of thyroid patients	
Rarely	12 (2.8)
Weekly	59 (14.0)
Daily	352 (83.2)
Treatment of patients with hypothyroidism	
Rarely	7 (1.7)
10 to 50 patients/year	34 (8.0)
51 to 100 patients/year	48 (11.3)
> 100 patients/year	334 (79.0)

*the sum of percentages exceeds 100% because > 1 option may have been selected; **other specialties (n > 3): diabetes, surgery, paediatrics, nephrology; ***Number of members in good standing (who paid recent fees); ****among them provisional and honorary members of the Polish Society of Endocrinology (who did not pay recent fees); *****The vast majority combined basic research with clinical practice. Only 3 respondents were clinically not active

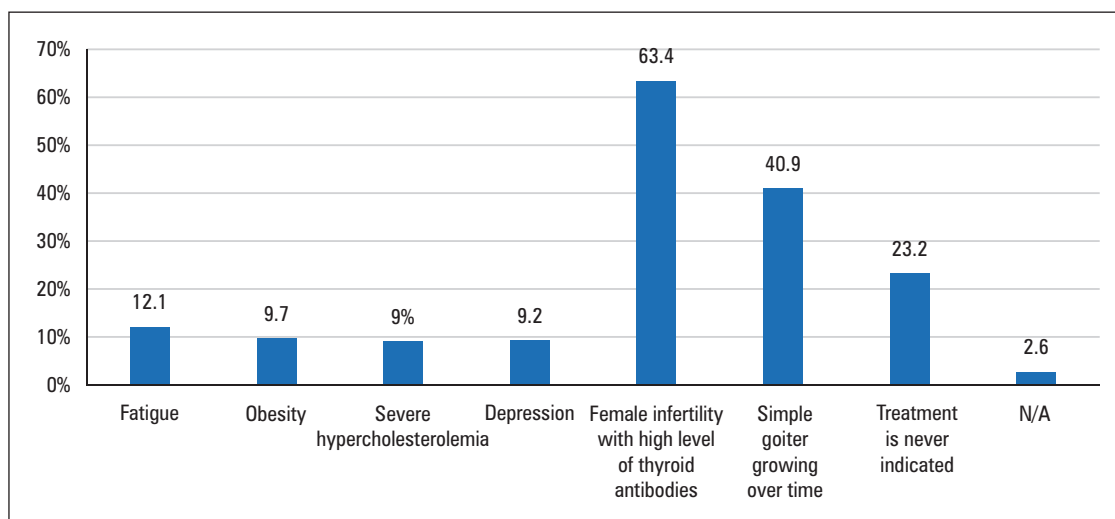


Figure 1. Use of thyroid hormones in euthyroid subjects. N/A (not applicable) — respondents who did not provide an answer; *The sum of percentages exceeds 100% because > 1 option may have been selected

Table 3. Use of thyroid hormones in clinical practice

	LT4 n (%)	LT3 n (%)	DTE n (%)	LT4 and LT3 combination n (%)	N/A n (%)
First choice for the treatment of hypothyroid patients	406 (96.0)	1 (0.2)	0	0	16 (3.8%)
Thyroid hormones prescribed in clinical practice*	406 (96.0)	7 (1.7)	0	128 (30.3)	17 (4.0%)

DTE — desiccated thyroid extracts; LT4 — levothyroxine; LT3 — liothyronine; N/A (not applicable) — respondents who did not provide an answer; *The sum of percentages exceeds 100% because > 1 option may have been selected

(age > 40 vs. ≤ 40, 41.0% vs. 11.0%; years in practice > 10 vs. ≤ 10, 38.1% vs. 10.5%; > 100 patients/year vs. ≤ 100 patients/year, 37.4% vs. 11.3%; χ^2 test, $p < 0.0001$) than those without these characteristics.

A high proportion of responders (390 of 423, 92.2%) indicated that most of their patients were treated with the type of LT4 that they prescribed, suggesting that physicians in Poland are able to dictate the formulation of LT4 dispensed.

Using different LT4 formulations

In all clinical situations, the majority of physicians preferred LT4 tablets or did not expect “major changes with different LT4 formulations” (Tab. 4). Among alternative formulations, LT4 as a liquid solution was preferred in some patients (110 of 423, 26.0%) who were unable to take LT4 in the fasting state and in patients with celiac disease, malabsorption, lactose intolerance, or intolerance to excipients (84 of 423, 19.9%). LT4 as soft gel capsules (which were not available in Poland at the time of the survey) were rarely chosen (less than 13% of respondents). Around a quarter of the respondents (109 of 423, 25.8%) chose alternative new

formulations (liquid solution or soft-gel capsules) for patients on LT4 who had unexplained poor biochemical control of hypothyroidism, while almost half (201 of 423, 47.5%) recommended LT4 from another manufacturer. Finally, 194 of 423 physicians (45.9%) expected no major changes in patients’ symptoms with the different formulations in patients treated with LT4 tablets, who, despite good biochemical control of hypothyroidism, had persistent symptoms, and 145 of 423 (34.4%) would prescribe LT4 tablets from another manufacturer in this situation.

Monitoring of thyroid hormone treatment

After starting LT4 replacement treatment, 241 of 423 respondents (57%) would recheck TSH after 8 weeks and 132 of 423 (31.2%) after 4–6 weeks. After switching from one formulation to another or from one manufacturer’s LT4 tablet to another, 180 of 423 physicians (42.6%) would recheck TSH after 4–6 weeks and 146 of 423 (34.5%) after 8 weeks, while only few (37 of 423, 8.7%) stated that there was no need to check thyroid function after changes in LT4 preparations, if the dosage was the same.

Table 4. *Levothyroxine (LT4) formulations preferred by respondents in different clinical scenarios*

	Tablets n (%)	Soft-gel capsules n (%)	Liquid solution n (%)	"I expect no major changes with different formulations" n (%)	N/A n (%)
Interfering drugs may influence the stability of therapy. Which LT4 preparation is, in your experience, least likely to be subject to variable absorption?	143 (33.8)	25 (5.9)	63 (14.9)	165 (39.0)	27 (6.4)
Choice of LT4 formulation in patient who self-reports intolerance to various foods, raising the possibility of celiac disease, malabsorption, lactose intolerance, or intolerance to common excipients	169 (40.0)	35 (8.3)	84 (19.9)	102 (24.1)	33 (7.8)
Choice of LT4 formulation for patient established on LT4 tablets, who has unexplained poor biochemical control of hypothyroidism	201 (47.5)*	38 (9.0)	71 (16.8)	73 (17.3)	40 (9.5)
Choice of LT4 formulation for patient with poor biochemical control, who is unable (due to busy lifestyle) to take LT4 fasted and separate from food/drink	110 (26.0)	52 (12.3)	110 (26.0)	106 (25.1)	45 (10.6)
Patient established on LT4, who has good biochemical control of hypothyroidism but continues to have symptoms	145 (34.3)*	17 (4.0)	20 (4.7)	194 (45.9)	47 (11.1)

N/A (not applicable) — respondents who did not provide an answer; *tablets from another manufacturer

Dietary supplements and combination treatment with LT4 + LT3

The majority of respondents considered prescribing dietary supplements (such as selenium and iodine) in addition to thyroid hormone replacement in hypothyroid patients with coexisting autoimmune thyroiditis (125 of 423, 29.6%) or at the patient's request (136 of 423, 32.2%). On the other hand, almost one in five (77 of 423, 18.2%) would never use dietary supplements. The use of supplements did not correlate with physicians' age.

LT4 + LT3 combination therapy was considered by 136 of 423 respondents (32.2%) when symptoms persisted notwithstanding normal TSH concentration, although a similar percentage (120 of 423, 28.4%) stated that available evidence does not support combination treatment (Fig. 2). Physicians aged ≤ 40 years more often stated that combined T4 + T3 treatment should never be used when compared to older colleagues (44.3% vs. 28.2%; $p = 0.003$).

Perceptions about persistence of hypothyroid symptoms despite normal serum TSH

Four questions in the survey referred to patients with LT4-treated hypothyroidism and persistent symptoms despite normal serum TSH. This was observed in less than 5% of patients by 33.1% (140 of 423) of respondents and in 6–10% of patients by 28.8% (122 of 423). Moreover, 36.4% (154 of 423) stated that they were seeing more such cases, whereas 28.1% (119 of 423) observed

no change. The majority of physicians considered comorbidities (285 of 423, 67.4%), psychosocial factors (278 of 423, 65.7%), and the burden of chronic disease (264 of 423, 62.4%) as most likely causes for persistent symptoms (Fig. 3). Just over half of the respondents (223 of 423, 52.7%) disagreed with the statement that LT4 treatment was unable to restore normal physiology. Ranking of potential causes for persistent symptoms despite normal serum TSH is presented in Table 5. Subgroup analysis suggested that younger physicians (≤ 40 years old) considered more frequently "patient unrealistic expectations" (96.2% vs. 87.2%; $p = 0.011$) and "psychosocial factors" (99.0% vs. 87.9%; $p = 0.001$) as a likely cause of persistent symptoms. Respondents who treated thyroid patients on a daily basis more often disagreed with the statement that the presence of underlying inflammation due to autoimmunity was responsible for persistent symptoms (36.7% vs. 22.5%; $p = 0.03$). Physicians who believed that persistent symptoms are not due to the inability of LT4 to restore normal physiology were less likely to prescribe combination LT4 + LT3 than physicians who believed that LT4 does not restore normal physiology (32.7% vs. 46.4%, χ^2 test, $p = 0.04$).

Respondents with diagnosed hypothyroidism

Sixty-one of 423 physicians (14.6%) declared having a diagnosis of hypothyroidism requiring thyroid hormone treatment. Among these, 26 (42.6%) experienced

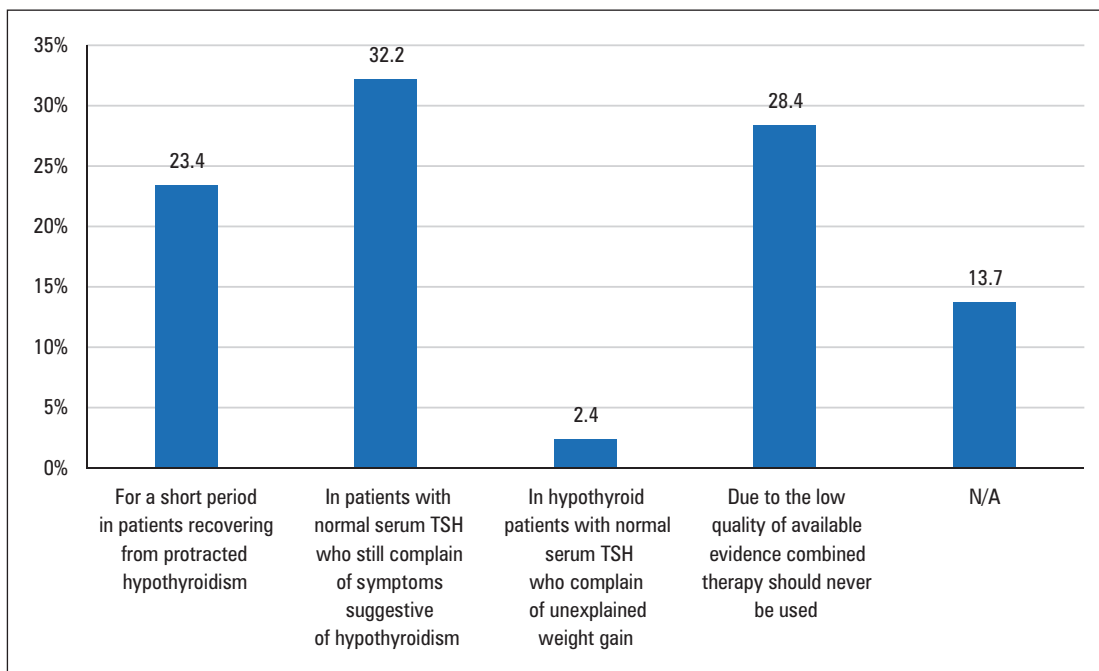


Figure 2. Levothyroxine (LT4) and liothyronine (LT3) combination therapy in patients with hypothyroidism. N/A (not applicable) — respondents who did not provide an answer

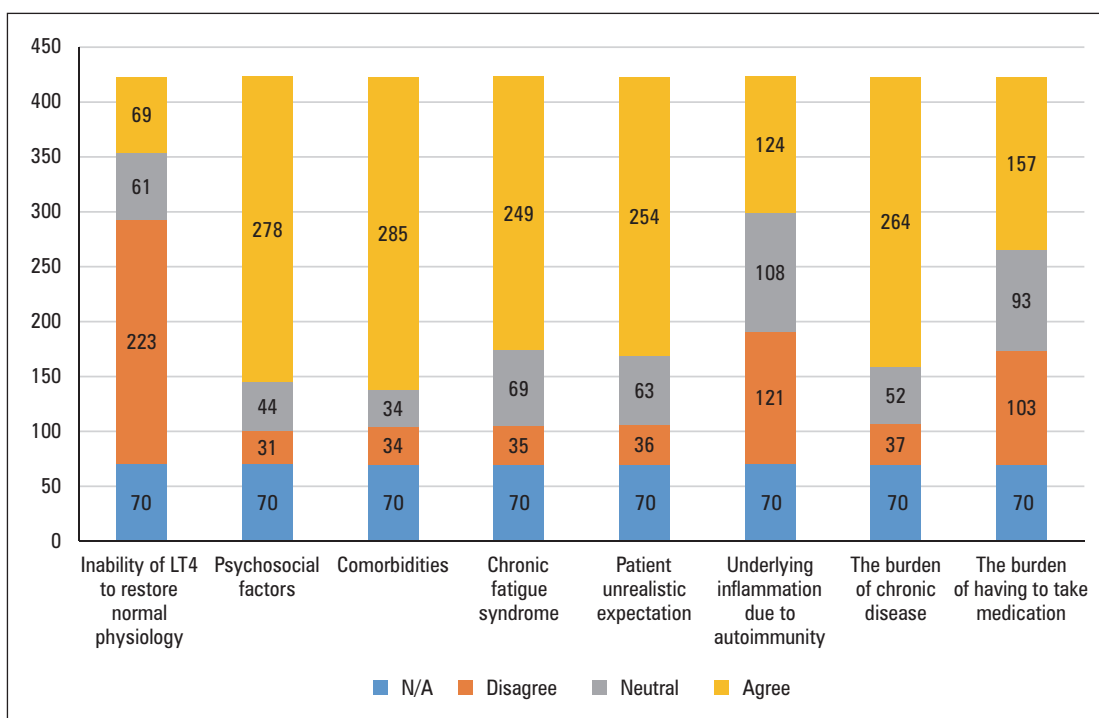


Figure 3. Physician-perceived causes for persistent symptoms in patients with hypothyroidism treated with levothyroxine, despite normal thyroid-stimulating hormone (TSH) levels. N/A (not applicable) — respondents who did not provide an answer

excessive tiredness/fatigue, 8 (13.1%) had tried LT4 and LT3 combination therapy, and 2 (3.3%) had tried DTE. Six physicians did not report any clinical improvement during LT4 + LT3 or DTE treatment, and 2 experienced “more energy”. Tachycardia (n = 1) and “hot flushes”

(n = 1) were reported side effects during LT4 and LT3 combination therapy. Only 50 of 423 physicians (11.8%) would consider LT4 + LT3 or DTE for themselves if they were to develop hypothyroidism. Nonetheless, 54 of 224 (24.1%) physicians who would not consider T4 + T3 or

Table 5. Ranked probable causes of persistent symptoms in patients with hypothyroidism treated with levothyroxine, despite normal thyroid-stimulating hormone (TSH) levels

Ranking in order of importance	Physician-perceived causes
1.	Comorbidities
2.	Psychosocial factors
3.	The burden of chronic disease
4.	Chronic fatigue syndrome
5.	Patient's unrealistic expectations
6.	Presence of underlying inflammation due to autoimmunity
7.	The burden of having to take medication
8.	Inability of levothyroxine to restore normal physiology

In Table 5, the ranking of 1 is the most likely and 8 the least likely cause. 109 of 423 (25.8%) respondents did not provide an answer. Calculated mean rankings were: 3.85, 3.9, 4.11, 4.17, 4.21, 5.14, 5.57, and 5.76, respectively

DTE for themselves if they became hypothyroid were prescribing it in their clinical practice.

Discussion

This is the first survey documenting attitudes of Polish physicians related to treatment of hypothyroidism. A total of 774 members of the Polish Society of Endocrinology were invited to participate in a web-based online THESIS questionnaire, of whom 423 (54.6%) completed the compulsory demographic data. The majority of respondents were specialists in endocrinology (367 of 423, 86.8%), treating thyroid patients on a daily basis. According to the Supreme Medical Chamber (Naczelna Izba Lekarska, <https://nil.org.pl/>), there were 1566 registered endocrinologists in Poland in 2020. Therefore, our survey reflected the opinion of 23.4% (367 of 1566) of Polish endocrinologists in all age groups, working in the public and the private sector of the health care system.

Clinical indications for treatment with thyroid hormones

In accordance with current guidelines, LT4 remains the treatment of choice for hypothyroidism in Poland. This was in agreement with other national THESIS investigations in Bulgaria, Denmark, and Italy [22–24]. However, some important deviations from evidence-based practice concerning indications for treatment with thyroid hormones were noted. Contrary to evidence from large randomized clinical trials, the majority of respondents (63.4%) would consider LT4 treatment in euthyroid females with chronic autoimmune thyroiditis and infertility [25, 26]. Due to frequent iodine deficiency in

Polish pregnant females, recommendations of iodine intake throughout the pregnancy and LT4 treatment (including patients with elevated thyroid autoantibodies) will be addressed in the national guidelines on the management of thyroid diseases in pregnancy, which will be updated in 2021 [27]. A significant proportion of physicians (40.3%) would also treat a simple goitre growing over time. Although treatment of benign euthyroid goitre is listed as a therapeutic indication for LT4, the available evidence indicates that: (i) the reduction of goitre size in patients treated with TSH-lowering doses of LT4 is only modest and most individuals are ineligible for this treatment [28]; (ii) the effect of LT4 is transient and ceases after drug withdrawal, in contrast to radioiodine [29]; and (iii) exogenous subclinical hyperthyroidism may be associated with serious adverse effects (including osteoporosis [30] and cardiovascular adverse events [31, 32]). Finally, 1 in 10 respondents would inappropriately use thyroid hormones in euthyroid patients with unrelated illnesses (morbid obesity, severe depression, unexplained fatigue, and/or hypercholesterolaemia) [2, 10].

Choice of LT4 formulation

Respondents had little opportunity to use alternative LT4 formulations in their clinical practice, because of national market limitations, in opposition to Danish physicians, where liquid LT4 is a widely available treatment option [24]. An oral solution has been commercially available since the last quarter of 2020, and it is more expensive than LT4 tablets. Therefore, in all suggested clinical situations, the majority of physicians preferred LT4 tablets in order to achieve satisfactory control of hypothyroidism, and they did not expect “major changes with different LT4 formulations”. Around a quarter (26.0%) of respondents would use liquid LT4 in patients who were unable to take LT4 in the fasting state, and 19.9% in patients with malabsorption, which is in accordance with a recent Polish expert opinion on liquid LT4 usage [33]. However, the available evidence is scarce and the precise indications and cost-effectiveness of alternative LT4 formulations have yet to be defined [7].

International guidelines indicate that a switch between LT4 tablets (brand name or generic) should be avoided, and if necessary should be followed by re-evaluation of serum TSH after 4 to 6 weeks. A small proportion of respondents (8.7%) stated that there was no need for biochemical assessment of thyroid status after such changes if the dosage remained the same. Taking into consideration the poor availability of liquid solution and soft gel capsules at the time of the study, physicians' preferences should be reassessed after gaining easy access to alternative LT4 formulations.

Dietary supplements in the treatment of hypothyroidism

The majority of respondents considered prescribing dietary supplements in addition to thyroid hormone replacement in patients with coexisting autoimmune thyroiditis (29.6%), subclinical hypothyroidism (7.3%), or at the patients' request (32.2%). This clinical practice is partially in disagreement with current evidence-based practice guidelines, which state that the use of dietary supplements (including selenium and iodine) is not recommended in the management of hypothyroidism, especially in iodine-sufficient areas [2, 3]. Nevertheless, in clinical practice the trend to prescribe selenium in autoimmune thyroiditis is noticeable among physicians in Europe [34]. Although mandatory iodization of household salt in Poland has led to a sustainable optimization of iodine status in the general population, iodine supplementation is still necessary in pregnant women [35]. Poland is considered as a selenium deficient country, and this may partially explain the use of dietary supplements in clinical practice [36]. However, studies using selenium supplementation in chronic autoimmune thyroiditis, even though significantly reducing thyroid autoantibodies [37], did not show apparent improvement in the clinical course of the disease [38].

Use of combined replacement therapy

The use of combination therapy with LT4 + LT3 remains highly controversial, with conflicting results from published clinical trials. The available tablets in Poland containing LT4 + LT3 have an "unphysiological" high ratio of T4 to T3 (5:1), whereas it is assumed that thyroid hormone replacement should be provided as a 14:1 ratio of T4 to T3 [5,39]. LT3 preparations and DTE are not available in Poland; these medications may be accessible by ordering from other EU countries with a "cross-border prescription". Nevertheless, approximately 1 out of 3 respondents would use LT4 + LT3 combination therapy. Physicians older than 40 years, treating more than 100 hypothyroid patients per year, prescribed LT4 + LT3 more often compared to younger colleagues. This could imply that younger endocrinologists follow guidelines more rigorously; alternatively, older colleagues may be more willing to comply with patient requests for T3. The main indication for combination therapy was the persistence of symptoms suggesting hypothyroidism notwithstanding TSH within the normal range (32.2%). The same approach was shared by 43.2% of Italian and 24.2% of Bulgarian physicians [22, 23]. This is in keeping with international guidelines, provided other autoimmune diseases and comorbidities have been ruled out [2–4]. On the other hand, almost the same percentage (28.4%) would not expect any improvement from this therapy. Further

well-designed randomized clinical trials in selected patients with persistent symptoms are called for [39, 40].

An important part of the survey concerned the behaviour of physicians with hypothyroidism in relation to their own treatment. A minority of physician respondents with hypothyroidism (10 of 61, 16.3%) had tried LT4 and LT3 combination treatment or DTE, without any significant improvement. Also, a minority of respondents (11.8%) would consider LT4 + LT3 combination treatment or DTE for themselves if they were to develop hypothyroidism.

Perceptions about persistence of hypothyroid symptoms despite normal serum TSH

A subset of patients with hypothyroidism treated with LT4 report impaired quality of life compared to controls and are not satisfied with their current therapy or their physicians [11, 12]. Despite serum TSH levels within reference values, these patients complain of persistent symptoms, which they attribute to hypothyroidism, including problems with weight management, fatigue, memory impairment, and mood disturbances. Indeed, this phenomenon was observed in up to 10% of patients by the majority of respondents (61.9%). The majority of physicians attributed these symptoms to comorbidities (67.4%), psychosocial factors (65.7%), and/or the burden of chronic disease (62.4%). On the other hand, "inability of LT4 to restore normal physiology" was the least likely explanation for persistent symptoms, despite evidence indicating that T4 monotherapy may be associated with low serum T3 levels. A similar view is shared by Bulgarian physicians, except placing the burden of chronic diseases above the psychosocial factors [22]. The current knowledge on this subject is still limited and further studies are awaited.

Concluding remarks

Apart from clinical practice recommendations, country-specific factors (including the availability and costs of various preparations) influence the thyroid hormone therapy patterns. Moreover, certain areas of clinical practice were identified (the use of thyroid hormones in euthyroid subjects and the use of dietary supplements), which are not in accordance with current evidence or guidelines [22, 23, 13–15].

Acknowledgment

We are indebted to all the members of the Polish Society of Endocrinology who filled in the questionnaire. Dr. Stanislaw Zgliczyński is thanked for his help in translating the questionnaire, Dr. Klaudia Gutowska for her assistance in statistical analysis, and Dr. Dorota Filipowicz for the article proofreading.

References

- Taylor PN, Albrecht D, Scholz A, et al. Global epidemiology of hyperthyroidism and hypothyroidism. *Nat Rev Endocrinol*. 2018; 14(5): 301–316, doi: [10.1038/nrendo.2018.18](https://doi.org/10.1038/nrendo.2018.18), indexed in Pubmed: 29569622.
- Garber JR, Cobin RH, Gharib H, et al. American Association of Clinical Endocrinologists and American Thyroid Association Taskforce on Hypothyroidism in Adults. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. *Endocr Pract*. 2012; 18(6): 988–1028, doi: [10.4158/EP12280.GL](https://doi.org/10.4158/EP12280.GL), indexed in Pubmed: 23246686.
- Guglielmi R, Frasoldati A, Zini M, et al. ITALIAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS STATEMENT-REPLACEMENT THERAPY FOR PRIMARY HYPOTHYROIDISM: A BRIEF GUIDE FOR CLINICAL PRACTICE. *Endocr Pract*. 2016; 22(11): 1319–1326, doi: [10.4158/EP161308.OR](https://doi.org/10.4158/EP161308.OR), indexed in Pubmed: 27482609.
- Jonklaas J, Bianco AC, Bauer AJ, et al. American Thyroid Association Task Force on Thyroid Hormone Replacement. Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. *Thyroid*. 2014; 24(12): 1670–1751, doi: [10.1089/thy.2014.0028](https://doi.org/10.1089/thy.2014.0028), indexed in Pubmed: 25266247.
- Wiersinga WM, Duntas L, Fadeyev V, et al. 2012 ETA Guidelines: The Use of L-T4 + L-T3 in the Treatment of Hypothyroidism. *Eur Thyroid J*. 2012; 1(2): 55–71, doi: [10.1159/000339444](https://doi.org/10.1159/000339444), indexed in Pubmed: 24782999.
- Chiovato L, Magri F, Carlé A. Hypothyroidism in Context: Where We've Been and Where We're Going. *Adv Ther*. 2019; 36(Suppl 2): 47–58, doi: [10.1007/s12325-019-01080-8](https://doi.org/10.1007/s12325-019-01080-8), indexed in Pubmed: 31485975.
- Nagy EV, Perros P, Papini E, et al. New Formulations of Levothyroxine in the Treatment of Hypothyroidism: Trick or Treat? *Thyroid*. 2021; 31(2): 193–201, doi: [10.1089/thy.2020.0515](https://doi.org/10.1089/thy.2020.0515), indexed in Pubmed: 33003978.
- Ruchala M, Szczepanek-Parulska E, Zybek A. The influence of lactose intolerance and other gastro-intestinal tract disorders on L-thyroxine absorption. *Endokrynol Pol*. 2012; 63(4): 318–323, indexed in Pubmed: 22933169.
- Virili C, Antonelli A, Santaguida MG, et al. Gastrointestinal Malabsorption of Thyroxine. *Endocr Rev*. 2019; 40(1): 118–136, doi: [10.1210/er.2018-00168](https://doi.org/10.1210/er.2018-00168), indexed in Pubmed: 30476027.
- Biondi B, Wartofsky L. Treatment with thyroid hormone. *Endocr Rev*. 2014; 35(3): 433–512, doi: [10.1210/er.2013-1083](https://doi.org/10.1210/er.2013-1083), indexed in Pubmed: 24433025.
- Mitchell AL, Hegedüs L, Žarković M, et al. Patient satisfaction and quality of life in hypothyroidism: An online survey by the british thyroid foundation. *Clin Endocrinol (Oxf)*. 2021; 94(3): 513–520, doi: [10.1111/cen.14340](https://doi.org/10.1111/cen.14340), indexed in Pubmed: 32978985.
- Peterson SJ, Cappola AR, Castro MR, et al. An Online Survey of Hypothyroid Patients Demonstrates Prominent Dissatisfaction. *Thyroid*. 2018; 28(6): 707–721, doi: [10.1089/thy.2017.0681](https://doi.org/10.1089/thy.2017.0681), indexed in Pubmed: 29620972.
- Jonklaas J, Tefera E, Shara N. Short-Term Time Trends in Prescribing Therapy for Hypothyroidism: Results of a Survey of American Thyroid Association Members. *Front Endocrinol (Lausanne)*. 2019; 10: 31, doi: [10.3389/fendo.2019.00031](https://doi.org/10.3389/fendo.2019.00031), indexed in Pubmed: 30761091.
- Burch HB, Burman KD, Cooper DS, et al. A 2013 survey of clinical practice patterns in the management of primary hypothyroidism. *J Clin Endocrinol Metab*. 2014; 99(6): 2077–2085, doi: [10.1210/jc.2014-1046](https://doi.org/10.1210/jc.2014-1046), indexed in Pubmed: 24527720.
- Frank R, Mamdani M, Wilby K. Cross-national comparison of levothyroxine utilization in four developed countries. *J Health Spec*. 2014; 2(4): 152, doi: [10.4103/1658-600x.142785](https://doi.org/10.4103/1658-600x.142785).
- Taylor PN, Iqbal A, Minassian C, 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(1): 32–39, doi: [10.1001/jamainternmed.2013.11312](https://doi.org/10.1001/jamainternmed.2013.11312), indexed in Pubmed: 24100714.
- Razvi S, Korevaar TIM, Taylor P. Trends, Determinants, and Associations of Treated Hypothyroidism in the United Kingdom, 2005–2014. *Thyroid*. 2019; 29(2): 174–182, doi: [10.1089/thy.2018.0251](https://doi.org/10.1089/thy.2018.0251), indexed in Pubmed: 30501570.
- Ernst FR, Barr P, Elmor R, et al. The Economic Impact of Levothyroxine Dose Adjustments: the CONTROL HE Study. *Clin Drug Investig*. 2017; 37(1): 71–83, doi: [10.1007/s40261-016-0462-3](https://doi.org/10.1007/s40261-016-0462-3), indexed in Pubmed: 27798756.
- Elmor R, Sandulli W, Carter C. The Economic Impact of Changing Levothyroxine Formulations in Difficult-to-Treat Hypothyroid Patients: An Evidence-Based Model. *Pharmacoeconomics: Open Access*. 2017; 2(2), doi: [10.4172/2472-1042.1000113](https://doi.org/10.4172/2472-1042.1000113).
- Khandelwal N, Johns B, Hepp Z, et al. The economic impact of switching from Synthroid for the treatment of hypothyroidism. *J Med Econ*. 2018; 21(5): 518–524, doi: [10.1080/13696998.2018.1443110](https://doi.org/10.1080/13696998.2018.1443110), indexed in Pubmed: 29458287.
- Jonklaas J, Tefera E, Shara N. Physician Choice of Hypothyroidism Therapy: Influence of Patient Characteristics. *Thyroid*. 2018; 28(11): 1416–1424, doi: [10.1089/thy.2018.0325](https://doi.org/10.1089/thy.2018.0325), indexed in Pubmed: 30289349.
- Use of Thyroid Hormones in Hypothyroid and Euthyroid Patients: a THESIS* Questionnaire Survey of Bulgarian Physicians | Българско дружество по ендокринология. <https://endo-bg.com/en/prilozhenie-na-hormonite-na-shitovidnata-zhleza-pri-hipotireoidni-i-eutireoidni-patsienti-anketno-prouchvane-thesis-sred-balgarski-lekari/> (March 31, 2021).
- Negro R, Attanasio R, Nagy EV, et al. Use of Thyroid Hormones in Hypothyroid and Euthyroid Patients; the 2019 Italian Survey. *Eur Thyroid J*. 2020; 9(1): 25–31, doi: [10.1159/000502057](https://doi.org/10.1159/000502057), indexed in Pubmed: 32071899.
- Riis KR, Frølich JS, Hegedüs L, 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 [Epub ahead of print], doi: [10.1007/s40618-021-01555-y](https://doi.org/10.1007/s40618-021-01555-y), indexed in Pubmed: 33774809.
- Dhillon-Smith RK, Middleton LJ, Sunner KK, et al. Levothyroxine in Women with Thyroid Peroxidase Antibodies before Conception. *N Engl J Med*. 2019; 380(14): 1316–1325, doi: [10.1056/NEJMoa1812537](https://doi.org/10.1056/NEJMoa1812537), indexed in Pubmed: 30907987.
- Wang H, Gao H, Chi H, et al. Effect of Levothyroxine on Miscarriage Among Women With Normal Thyroid Function and Thyroid Autoimmunity Undergoing In Vitro Fertilization and Embryo Transfer: A Randomized Clinical Trial. *JAMA*. 2017; 318(22): 2190–2198, doi: [10.1001/jama.2017.18249](https://doi.org/10.1001/jama.2017.18249), indexed in Pubmed: 29234808.
- Hubalewska-Dydejczyk A, Lewiński A, Milewicz A, et al. Management of thyroid diseases during pregnancy. *Endokrynol Pol*. 2011; 62(4): 362–381, indexed in Pubmed: 21879479.
- Fast S, Bonnema SJ, Hegedüs L. The majority of Danish nontoxic goitre patients are ineligible for Levothyroxine suppressive therapy. *Clin Endocrinol (Oxf)*. 2008; 69(4): 653–658, doi: [10.1111/j.1365-2265.2008.03241.x](https://doi.org/10.1111/j.1365-2265.2008.03241.x), indexed in Pubmed: 18363890.
- Bonnema SJ, Hegedüs L. Radioiodine therapy in benign thyroid diseases: effects, side effects, and factors affecting therapeutic outcome. *Endocr Rev*. 2012; 33(6): 920–980, doi: [10.1210/er.2012-1030](https://doi.org/10.1210/er.2012-1030), indexed in Pubmed: 22961916.
- Abrahamsen Bo, Jørgensen HL, Laulund AS, et al. The excess risk of major osteoporotic fractures in hypothyroidism is driven by cumulative hyperthyroid as opposed to hypothyroid time: an observational register-based time-resolved cohort analysis. *J Bone Miner Res*. 2015; 30(5): 898–905, doi: [10.1002/jbmr.2416](https://doi.org/10.1002/jbmr.2416), indexed in Pubmed: 25431028.
- Lillevang-Johansen M, Abrahamsen Bo, Jørgensen HL, et al. Duration of Hyperthyroidism and Lack of Sufficient Treatment Are Associated with Increased Cardiovascular Risk. *Thyroid*. 2019; 29(3): 332–340, doi: [10.1089/thy.2018.0320](https://doi.org/10.1089/thy.2018.0320), indexed in Pubmed: 30648498.
- Gharib H, Papini E, Garber JR, et al. AACE/ACE/AME Task Force on Thyroid Nodules. American Association Of Clinical Endocrinologists, American College Of Endocrinology, And Associazione Medici Endocrinologi Medical Guidelines For Clinical Practice For The Diagnosis And Management Of Thyroid Nodules — 2016 Update. *Endocr Pract*. 2016; 22(5): 622–639, doi: [10.4158/EP161208.GL](https://doi.org/10.4158/EP161208.GL), indexed in Pubmed: 27167915.
- Gietka-Czernel M, Hubalewska-Dydejczyk A, Kos-Kudła B, et al. Expert opinion on liquid L-thyroxine usage in hypothyroid patients and new liquid thyroxine formulation — Tirosint SOL. *Endokrynol Pol*. 2020; 71(5): 441–465, doi: [10.5603/EPa2020.0065](https://doi.org/10.5603/EPa2020.0065), indexed in Pubmed: 33202031.
- Winther KH, Papini E, Attanasio R, et al. A 2018 European Thyroid Association Survey on the Use of Selenium Supplementation in Hashimoto's Thyroiditis. *Eur Thyroid J*. 2020; 9(2): 99–105, doi: [10.1159/000504781](https://doi.org/10.1159/000504781), indexed in Pubmed: 32257959.
- Trofimiuk-Müldner M, Konopka J, Sokołowski G, et al. Current iodine nutrition status in Poland (2017): is the Polish model of obligatory iodine prophylaxis able to eliminate iodine deficiency in the population? *Public Health Nutr*. 2020; 23(14): 2467–2477, doi: [10.1017/S1368980020000403](https://doi.org/10.1017/S1368980020000403), indexed in Pubmed: 32476639.
- Ambroziak U, Hybsier S, Shahnazaryan A, et al. Severe selenium deficits in pregnant women irrespective of autoimmune thyroid disease in an area with marginal selenium intake. *J Trace Elem Med Biol*. 2017; 44: 186–191, doi: [10.1016/j.jtemb.2017.08.005](https://doi.org/10.1016/j.jtemb.2017.08.005), indexed in Pubmed: 28965575.
- Wichman J, Winther KH, Bonnema SJ, et al. Selenium Supplementation Significantly Reduces Thyroid Autoantibody Levels in Patients with Chronic Autoimmune Thyroiditis: A Systematic Review and Meta-Analysis. *Thyroid*. 2016; 26(12): 1681–1692, doi: [10.1089/thy.2016.0256](https://doi.org/10.1089/thy.2016.0256), indexed in Pubmed: 27702392.
- Winther KH, Rayman MP, Bonnema SJ, et al. Selenium in thyroid disorders - essential knowledge for clinicians. *Nat Rev Endocrinol*. 2020; 16(3): 165–176, doi: [10.1038/s41574-019-0311-6](https://doi.org/10.1038/s41574-019-0311-6), indexed in Pubmed: 32001830.
- Jonklaas J, Bianco AC, Cappola AR, et al. Evidence-Based Use of Levothyroxine/Liothyronine Combinations in Treating Hypothyroidism: A Consensus Document. *Eur Thyroid J*. 2021; 10(1): 10–38, doi: [10.1159/000512970](https://doi.org/10.1159/000512970), indexed in Pubmed: 33777817.
- Wiersinga WM. T4 + T3 combination therapy: any progress? *Endocrine*. 2019; 66(1): 70–78, doi: [10.1007/s12020-019-02052-2](https://doi.org/10.1007/s12020-019-02052-2), indexed in Pubmed: 31617166.