








Differences in thyroid hormone prescribing practices between Japan Thyroid Association-certified thyroid specialists and non-certified members: a nationwide survey in Japan

Yuji Nagayama¹ , Junichi Tajiri², Tsukasa Murakami³ , Natsuko Watanabe⁴ , Shinya Sato¹ , Hisakazu Shindo¹ , Seigo Tachibana¹ , Roberto Attanasio⁵, Enrico Papini⁶, Petros Perros⁷, Endre V. Nagy⁸, Laszlo Hegedüs⁹, Koichi Ito⁴ and Hiroyuki Yamashita¹ 

¹ Departments of Endocrinology and Surgery, Yamashita Thyroid Hospital, Fukuoka, Japan

² Tajiri Thyroid Clinic, Kumamoto, Japan

³ Department of Endocrinology, Noguchi Thyroid Clinic and Hospital Foundation, Oita, Japan

⁴ Departments of Internal Medicine and Surgery, Ito Hospital, Tokyo, Japan

⁵ Scientific Committee, Associazione Medici Endocrinologi, Milan, Italy

⁶ Department of Endocrinology and Metabolism, Regina Apostolorum Hospital, Lifenet Health Group, Rome, Italy

⁷ Institute of Translational and Clinical Research, Newcastle University, Newcastle upon Tyne, United Kingdom

⁸ Division of Endocrinology, Department of Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

⁹ Department of Endocrinology, Odense University Hospital, Odense C, Denmark

Abstract. Thyroid hormone (TH) prescribing practices, particularly on hypothyroid and euthyroid patients, were compared between Japan Thyroid Association (JTA)-certified thyroid specialists and non-certified members. A nationwide questionnaire survey (Treatment of Hypothyroidism in Europe by Specialists: An International Survey) was conducted among all 2,938 JTA members, including 874 certified specialists and 2,064 non-certified members, to assess self-reported TH prescription choices in various clinical scenarios. Responses from certified specialists and non-certified members were statistically compared. A total of 207 certified specialists (23.7%) and 129 non-certified members (6.3%) responded and completed the questionnaire. Although all certified specialists and non-certified members selected levothyroxine (LT4) as first-line therapy for hypothyroidism, certified specialists more often used liothyronine (LT3) plus LT4 combination therapy than non-certified members (28% vs. 12%, $p < 0.001$), particularly for LT4-treated patients with persistent hypothyroid-like symptoms (9% vs. 2%, $p = 0.02$). For euthyroid individuals, 71% of certified specialists and 60% of non-certified members considered TH treatment ($p = 0.043$). Non-certified members who see >100 hypothyroid patients per year were more inclined to use combination therapy for hypothyroid patients and TH for euthyroid patients than those of ≤ 100 patients ($p < 0.049$ and 0.001 , respectively). In conclusion, JTA-certified thyroid specialists and non-certified members exhibit distinct TH prescribing patterns. Certified specialists are more open to combination therapy and treating selected euthyroid patients, whereas non-certified members favor guideline-based LT4 monotherapy. These differences underscore the impact of specialization on clinical practice and suggest a need for updated guidelines and targeted education to rationalize thyroid care.

Key words: THESIS questionnaire, JTA-certified thyroid specialists, Non-certified members, Hypothyroidism, Thyroid hormones

Introduction

Primary hypothyroidism is a prevalent endocrine disorder, most often caused by Hashimoto's thyroiditis in

iodine-sufficient regions such as Japan [1]. Lifelong levothyroxine (LT4) replacement is the standard therapy. However, 10–20% of patients report persistent hypothyroid-like symptoms despite normalization of TSH on LT4 replacement therapy [2], prompting interest in substitution with liothyronine (LT3) or LT3 + LT4 combination therapy in such patients. Although some studies suggest their possible benefits in selected patients [2, 3], randomized trials have not demonstrated consistent superiority over LT4 monotherapy [2, 4], and guidelines from American

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Correspondence to: Yuji Nagayama, MD, PhD, Departments of Endocrinology and Surgery, Yamashita Thyroid Hospital, 1-8 Shimo-Gofuku-machi, Hakata-ku, Fukuoka 812-0034, Japan.

E-mail: yuji.nagayama@kojosen.com

Thyroid Association (ATA) and European Thyroid Association (ETA), although published over 10 years ago, recommend LT4 alone [5, 6]. The 2021 ATA/British Thyroid Association (BTA)/ETA joint consensus addressed the controversial use of LT3 + LT4 combination therapy in hypothyroidism, proposing that for patients who are dissatisfied with LT4 (*e.g.*, residual symptoms, no improvement in quality of life), the efficacy of combination therapy must be verified in appropriately designed new clinical trials, but still concluded that LT4 remains the standard treatment at present [7]. Our understanding of why such patients have persistent symptoms remains poor, but recent studies have focused on these symptoms, also labeled “medically not yet explained symptoms” being, at least in part, explained by behavioral traits such as somatization and type D personality [8–11]. Nevertheless, use of LT3 or combination therapy has increased in some countries [12]. Another concern is use of thyroid hormone (TH) in biochemically euthyroid individuals. Despite little supporting evidence, clinicians have been shown to consider LT4 for euthyroid individuals with hyperlipidemia [13], goiter [14], female infertility [15], and obesity [16].

THESIS (Treatment of hypothyroidism in Europe by specialists: an international survey) is a survey of European thyroid specialists exploring the use of TH for hypothyroid and euthyroid patients [17]. Several recent THESIS surveys have revealed wide variations in such practices across Europe, Australia, Latin America, Canada and Israel [17–21]. In Japan, we recently reported that the Japan Thyroid Association (JTA)-certified thyroid specialists almost universally use LT4 as first-line treatment, rarely use LT3 + LT4 combination therapy, yet still prescribe TH in selected euthyroid scenarios [22].

The JTA includes both board-certified thyroid specialists, who have undergone specific training and examination, and non-certified members. Clinical decision-making may differ between the two groups, yet comparative data are lacking. Therefore, this study aimed to compare TH prescribing practices between JTA-certified specialists and non-certified members, focusing on both hypothyroid and euthyroid patients, to clarify the influence of board-certification on clinical management.

Materials and Methods

The THESIS questionnaire survey

The Supplementary Table 1 shows the Japanese version of the THESIS questionnaire survey written in English [22]. The questionnaire was sent to all the 2,938 members of the JTA (including 874 certified thyroid specialists and 2,938 non-certified members). The JTA has certification systems for thyroid specialists and thyroid

specialty facilities [22]. Thyroid specialists certified by JTA fulfil the following conditions: (i) have been members of JTA for at least five years; (ii) have sufficient number of publications on clinical thyroid care published in medical journals or presented at the JTA annual conferences; (iii) have passed a written examination; and (iv) have been practicing thyroid medicine. The JTA-accredited thyroid specialty facilities (i) have JTA-certified thyroid specialists on their staff; (ii) provide sufficient outpatient thyroid care; and (iii) can carry out the laboratory tests necessary for thyroid care.

This study was approved by the Yamashita Thyroid Hospital Ethics Committee (approval no. 2024-8).

Statistical analyses

Descriptive statistics are presented as absolute numbers and percentages of the respondents for each question. Subgroup analyses were performed using Chi-squared test, Fisher’s exact test and multivariate logistic regression analysis to assess the associations between responses to each question (B 1 to 15) and demographic variables (A 1 to 9) (The Supplementary Table 1). For multivariate logistic regression, the following covariates were included: age (categorical: (i) 6 groups separated by 10-year intervals, and (ii) 3 groups of 24–40, 41–60 and >60 years), sex (categorical: male or female), years of medical practice (categorical: (i) 5 groups separated by 10-year intervals, and (ii) 2 groups of 1–30 and >30), working places (categorical: a specialty facility accredited by the JTA or not), frequency of medical practice (categorical: daily or weekly), and number of treated hypothyroid patients (categorical: (i) 3 groups of 10–50, 51–100 and >100, and (ii) 2 groups of 10–100 and >100). Prior to multivariate logistic regression analyses, the variance inflation factors (VIFs) for each demographic data were calculated to assess multicollinearity, and found <2.5 in all the analyses, indicating the absence of problematic multicollinearity. A two-sided $p < 0.05$ was considered significant. All statistical analyses were performed with EZR version 1.68 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) as previously described [23].

Results

Response rates

The response rates were 209/874 (23.9%) of certified thyroid specialists and 133/2,064 (6.4%) of the non-certified members, of which 207 (23.7%) and 129 (6.3%), respectively, provided consent to participate and completed all demographic questions (A1 to A9), and were analyzed in this study. The response rates in other countries/regions were 32.9% in Europe and 59% in Israel, 19.5% in Canada, 13% in Australia, and 18% in

South America [17-21]. The responses to the questions A1 to A9 and to the questions B1 to B15 are summarized in Tables 1, 2, respectively.

Readers may wish to refer to these two tables for detailed data. Since no significant differences were observed in the questions B2, B4, B6, B7 and B9–14, we mainly discuss the points of interest regarding the similarities and differences in TH prescription to euthyroid patients and use of T3 + T4 combination therapy between the two groups.

Demographic characteristics

As summarized in Table 1, the non-certified member respondents were younger and had shorter medical experience than certified specialists. In all JTA members, the largest age group was those in their 40s (Supplementary Table 2), while it was those in their 50s in certified specialists, and it was those aged 31 to 50 in non-certified members. Furthermore, the response rate appeared somewhat lower in female members. Compared to certified specialists, fewer non-certified members worked at JTA-accredited thyroid specialty facilities such as university

Table 1 Demographic characteristics of respondents (A1 to A9)

	Certified specialists*	Non-certified members	p-value
Number of respondents	207	129	
A1. Age			
24–30	0 (0)	4 (3.1)	<0.001**
31–40	13 (6.3)	35 (27.1)	
41–50	63 (30.4)	35 (27.1)	
51–60	66 (31.9)	31 (24.0)	
61–70	44 (21.3)	15 (11.6)	
>70	21 (10.1)	9 (7.0)	
A2. Gender			
Male	157 (75.8)	95 (73.6)	0.868
Female	49 (23.7)	33 (25.6)	
Unknown	1 (0.5)	1 (0.8)	
A3. Years in medical practice			
1–10	1 (0.5)	23 (17.8)	<0.001
11–20	45 (21.7)	34 (26.4)	
21–30	78 (37.7)	38 (29.5)	
31–40	50 (24.2)	16 (12.4)	
>40	33 (15.9)	18 (14.0)	
A4. Specialty (check all that apply)			
Endocrinology	173 (83.6)	96 (74.4)	<0.001
Internal medicine	55 (26.6)	45 (34.9)	0.317
Pediatrics	3 (1.4)	0 (0)	0.233
Pediatric endocrinology	6 (2.9)	8 (6.2)	0.405
Nuclear medicine	2 (1.0)	0 (0.0)	0.379
Surgery	33 (15.9)	12 (9.3)	0.002
Obstetrics and gynecology	0 (0.0)	0 (0.0)	1.000
Otolaryngology	9 (4.3)	6 (4.7)	0.439
Others	11 (5.3)	11 (8.5)	0.835
A5. Membership (domestic conferences) (check all that apply)			
Endocrine society	168 (81.2)	108 (83.7)	<0.001
Endocrine surgery	43 (20.8)	14 (10.9)	<0.001
Pediatric endocrinology	8 (3.9)	9 (7.0)	0.808
Otorhinolaryngology head and neck surgery	11 (5.3)	6 (4.7)	0.317
Nuclear medicine	7 (3.4)	0 (0.0)	0.033
Others	39 (18.8)	29 (22.5)	0.123

Table 1 Cont.

	Certified specialists*	Non-certified members	<i>p</i> -value
A6. Where do you practice? (check all that apply)			
University hospital	56 (27.1)	39 (30.2)	0.022
General hospital	76 (36.7)	63 (48.8)	0.270
Thyroid-specific hospital/clinic	73 (35.3)	25 (19.4)	<0.001
General clinic	30 (14.5)	25 (19.4)	0.423
Basic research	2 (1.0)	4 (3.1)	0.414
A7. Do you work in a specialty facility accredited by the JTA?			
Yes	144 (69.6)	38 (29.5)	<0.001
No	63 (30.4)	91 (70.5)	
A8. Do you treat thyroid patients on a regular basis (daily or weekly)?			
Yes, daily	143 (69.1)	64 (49.6)	<0.001
Yes, weekly	62 (30.0)	63 (48.8)	
No, rarely	2 (1.0)	2 (1.6)	
A9. Do you treat patients with hypothyroidism?			
Yes, 10–50 patients	44 (21.3)	49 (38.0)	<0.001
Yes, 51–100	42 (20.3)	36 (27.9)	
Yes, >100	119 (57.5)	42 (32.6)	
No, rarely	2 (1.0)	2 (1.6)	

*, The data on certified specialists are taken from ref. 13.

**, Bolds indicate statistical significances.

hospitals or thyroid specialty hospitals. In addition, non-certified members see thyroid patients less often, and treat a smaller number of hypothyroid patients per year than certified specialists.

Use of TH for patients with hypothyroidism

All certified specialists and non-certified members chose LT4 as the initial treatment for patients with hypothyroidism (question B2, Table 2). However, the rate of using LT3 + LT4 combination therapy in clinical practice was higher by certified specialists than by non-certified members (28.0% vs. 11.6%, $p < 0.001$) (B3). Furthermore, “combined therapy should never be used due to the low quality of available evidence” was the response by 68.6% of certified specialists vs. 77.5% of non-certified members ($p = 0.005$) (B8). These differences stem at least in part from a difference in the perceived frequency of LT3 + LT4 combination therapy being offered to patients established on LT4 replacement therapy who continue to exhibit hypothyroid-like symptoms (8.7% of certified specialists vs. 2.3% of non-certified members; $p = 0.020$) (B5).

Despite the significant difference in the rate of LT3 + LT4 prescription between the two groups, the perceived top three causes of persistent symptoms were shared by both groups: “psychological factors,” “comorbidities,” and “chronic fatigue syndrome,” whereas “inability of

levothyroxine to restore tissue euthyroidism” was ranked third and second from the bottom by certified specialists and non-certified members, respectively (B11, judged by the aggregate percentages of “agree” plus “strongly agree”). The multivariate analyses revealed that LT3 + LT4 combination therapy was supported by the respondents who see >100 hypothyroid patients per year, as compared to those who see ≤ 100 patients ($p = 0.009$). This is also true in non-certified members ($p = 0.02$), but not in certified specialists ($p = 0.194$).

Use of TH for euthyroid patients

As shown in Table 2, 40.3% of non-certified members would never use TH for euthyroid patients, as compared to 29.0% of certified specialists ($p = 0.043$) (B1). There were no significant differences in the rate of TH prescriptions for each disease listed in question B1, and for pregnant or infertile women with various TSH and thyroid antibody levels (B14 and 15). The multivariate analysis revealed again that the respondents who see >100 hypothyroid patients per year were more inclined to use TH for euthyroid patients than those who see ≤ 100 patients ($p < 0.001$). This is also true in non-certified members ($p = 0.036$), but not in certified specialists ($p = 0.092$).

Table 2 Summary of responses to the questions B1 to B15

	Certified specialists*	Non-certified members	p-value
Number of patients	207	129	
B1. Thyroid hormones may be indicated in biochemically euthyroid patients with: (check all that apply)			
No, treatment is never indicated for these patients	60 (29.0)	52 (40.3)	0.043**
Obesity resistant to life-style interventions	1 (0.5)	0 (0.0)	1.000
Severe hypercholesterolemia, as a complementary treatment	2 (1.0)	0 (0.0)	0.526
Depression resistant to anti-depressant medications	3 (1.4)	0 (0.0)	0.288
Female infertility with high level of thyroid antibodies	97 (46.9)	49 (38.0)	0.115
Simple goiter growing over time	38 (18.4)	15 (11.6)	0.124
Unexplained fatigue	6 (2.9)	3 (2.3)	1.000
Hashimoto's thyroiditis with a huge goiter	60 (29.0)	29 (22.5)	0.166
Differentiated thyroid cancer on active surveillance	37 (17.9)	18 (14.0)	0.367
Differentiated thyroid cancer that cannot be operated on for various reasons	34 (16.4)	18 (14.0)	0.642
B2. Which thyroid hormones should be the first choice for the treatment of hypothyroid patients?			
LT4 tablet	205 (99.0)	125 (96.9)	0.209
LT4 powder	2 (1.0)	4 (3.1)	
LT3 tablet	0 (0.0)	0 (0.0)	
LT3 + LT4 combination	0 (0.0)	(0.0)	
B3. Which of the following drugs are you prescribing in clinical practice? (check all that apply)			
LT4 tablet	207 (100.0)	129 (100.0)	1.000
LT4 powder	91 (44.0)	46 (35.7)	0.139
LT3 tablet	39 (18.8)	15 (11.6)	0.093
LT3 + LT4 combination	58 (28.0)	15 (11.6)	<0.001
B4. Which of the following would you prescribe for a patient established on LT4 who has abnormal blood tests (e.g., hypercholesterolemia)?			
No change	182 (87.9)	112 (86.8)	0.988
Increase LT4	21 (10.1)	14 (10.9)	
LT3 + LT4 combination	3 (1.5)	2 (1.6)	
LT3 monotherapy	1 (0.5)	1 (0.8)	
B5. Which of the following would you prescribe for a patient established on LT4 who continues to have symptoms?			
No change	146 (70.5)	97 (75.2)	0.402
Increase LT4	42 (20.3)	27 (21.1)	
LT3 + LT4 combination	18 (8.7)	3 (2.3)	(0.020)
LT3 monotherapy	1 (0.5)	1 (0.8)	
B6. After the start of LT4 replacement therapy, when would you re-check serum TSH?			
After 2 weeks	13 (6.3)	15 (11.6)	0.256
After 4 to 6 weeks	132 (63.8)	81 (62.8)	
After 8 weeks	21 (10.1)	8 (6.2)	
No, I mostly rely on clinical evaluation	41 (19.8)	25 (19.4)	
B7. Do you think that dietary supplements (such as selenium or iodine) may be used in addition to thyroid hormone replacement in hypothyroidism?			
When there is coexisting autoimmune thyroiditis	1 (0.5)	1 (0.8)	0.053
In subclinical hypothyroidism	2 (1.0)	0 (0.0)	
At the patient's request or as a complementary treatment	4 (1.9)	9 (7.0)	
No, dietary supplements should never be used	200 (96.6)	119 (92.2)	
B8. LT3 + LT4 combination therapy is generally not recommended. Do you think that may be considered:			
Due to the low quality of available evidence, combined therapy should never be used	142 (68.6)	100 (77.5)	0.364
For a short period, in patients recovering from protracted hypothyroidism	19 (9.2)	8 (6.2)	
In patients with normal serum TSH who still complain of symptoms suggestive of hypothyroidism	41 (15.2)	19 (14.7)	
In patients with normal serum TSH who complain of unexplained weight gain	0 (0.0)	0 (0.0)	
In patients with normal TSH who have abnormal blood tests (e.g., hypercholesterolemia)	5 (2.4)	2 (1.6)	
Due to the low quality of available evidence, combined therapy should never be used	142 (68.6)	100 (77.5)	0.005
Use combined therapy for one of the above four cases	65 (31.4)	29 (22.5)	

Table 2 Cont.

	Certified specialists*	Non-certified members	<i>p</i> -value
B9. It has been reported that some patients with hypothyroidism treated with LT4 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?			
≤5% of patients	123 (59.4)	73 (56.6)	0.470
6 to 10%	40 (19.3)	22 (17.1)	
11 to 30%	17 (8.2)	8 (6.2)	
>30%	1 (0.5)	1 (0.8)	
Not sure	26 (12.6)	25 (19.4)	
B10. In your experience what has been the trend over the past 5 years?			
I am seeing more such cases	13 (6.2)	9 (7.0)	0.115
I am seeing fewer such cases	1 (0.5)	0 (0.0)	
No change	125 (60.4)	63 (48.8)	
Not sure	68 (32.9)	57 (44.2)	
B11. In most patients treated with levothyroxine who achieve normal serum TSH, persistent symptoms are due to: (select an answer for each)			
Inability of levothyroxine to restore normal physiology			
Strongly disagree/Disagree	39 (18.8)	30 (23.2)	0.448
Neutral	94 (45.4)	61 (47.3)	
Strongly agree/Agree	72 (34.8)	38 (29.5)	
Psychological factors			
Strongly disagree/Disagree	8 (3.9)	7 (5.5)	0.822
Neutral	64 (30.9)	41 (31.8)	
Strongly agree/Agree	135 (65.2)	81 (62.8)	
Comorbidities			
Strongly disagree/Disagree	12 (5.8)	14 (11.0)	0.308
Neutral	83 (40.1)	51 (39.8)	
Strongly agree/Agree	109 (52.9)	163 (49.2)	
Chronic fatigue syndrome			
Strongly disagree/Disagree	13 (6.2)	18 (14.0)	0.101
Neutral	83 (40.1)	54 (41.9)	
Strongly agree/Agree	105 (50.7)	57 (44.2)	
Patient unrealistic expectation			
Strongly disagree/Disagree	24 (11.2)	20 (15.9)	0.705
Neutral	96 (48.4)	59 (46.8)	
Strongly agree/Agree	87 (42.0)	47 (37.3)	
Presence of underlying inflammation due to autoimmunity			
Strongly disagree/Disagree	33 (15.9)	21 (16.3)	0.479
Neutral	112 (54.1)	70 (54.3)	
Strongly agree/Agree	62 (30.0)	38 (29.5)	
The burden of chronic disease			
Strongly disagree/Disagree	27 (13.0)	18 (14.0)	0.884
Neutral	103 (49.8)	63 (48.8)	
Strongly agree/Agree	77 (37.2)	48 (37.3)	
The burden of having to take medication			
Strongly disagree/Disagree	38 (18.4)	34 (26.4)	0.305
Neutral	104 (50.2)	58 (45.0)	
Strongly agree/Agree	65 (31.4)	37 (28.7)	

Discussion

This nationwide survey provides novel insights into differences in TH prescribing between JTA-certified spe-

cialists and non-certified members. While both groups consistently selected LT4 as first-line therapy for hypothyroidism, their attitudes toward LT3 use diverged. Certified specialists were more willing to consider LT3 +

Table 2 Cont.

	Certified specialists*	Non-certified members	p-value
B12. Some patients treated with supraphysiological doses of thyroid hormones (leading to suppressed serum TSH, and elevated serum T4 and/or T3 concentrations) report a significant improvement in symptoms such as fatigue. What do you think is the most likely explanation for this observation? (Select an answer for each)			
Such patients have low tissue T3 levels, despite normal serum TSH and require high doses of thyroid hormones to restore normal health			
Strongly disagree/Disagree	20 (9.6)	12 (9.5)	0.257
Neutral	51 (24.6)	41 (32.3)	
Strongly agree/Agree	136 (65.7)	74 (58.2)	
The significant improvement is a placebo effect			
Strongly disagree/Disagree	31 (14.9)	28 (22.1)	0.561
Neutral	114 (55.1)	61 (48.0)	
Strongly agree/Agree	62 (30.0)	38 (30.0)	
High doses of thyroid hormones are euphoric for some patients			
Strongly disagree/Disagree	47 (22.7)	29 (22.5)	0.987
Neutral	101 (48.8)	59 (45.7)	
Strongly agree/Agree	59 (28.5)	39 (31.8)	
The improvement in symptoms is usually because the high doses of thyroid hormones help patients lose weight			
Strongly disagree/Disagree	64 (30.9)	36 (27.9)	0.884
Neutral	111 (53.6)	73 (56.6)	
Strongly agree/Agree	32 (15.5)	20 (15.5)	
B13. In an athyreotic patient after total thyroidectomy for thyroid cancer, who is ineligible for TSH suppressive therapy, and has subnormal serum FT3 despite normal TSH and FT4 on LT4 therapy, which of the following would you prescribe?			
No change	70 (33.8)	56 (43.4)	0.409
Increase LT4 to increase serum FT3 to the extent that the TSH value remains within the reference value	88 (42.5)	51 (39.5)	
Increase LT4 until FT3 normalizes, regardless of the TSH level.	34 (16.4)	14 (10.9)	
Change to LT3	2 (1.0)	1 (0.8)	
LT3 + LT4 combination	13 (6.2)	7 (5.4)	
B14. In a pregnant woman without previous history of hypothyroidism and uncomplicated obstetric history, when would you usually recommend treatment with LT4? (check all that apply).			
4 > TSH \geq 2.5 mU/L and negative thyroid antibodies	89 (43.0)	54 (41.9)	0.910
4 > TSH \geq 2.5 mU/L and positive thyroid antibodies	159 (76.8)	103 (78.8)	0.568
10 mU/L > TSH \geq 4 mU/L	171 (82.6)	100 (77.5)	0.259
TSH \geq 10 mU/L	184 (88.9)	107 (82.9)	0.139
Low FT4 with normal TSH	52 (25.1)	41 (31.8)	0.210
A case-by-case basis, taking into consideration the history of infertility treatment, miscarriage, and other factors	135 (72.5)	80 (62.0)	0.561
B15. In a woman who wants to conceive, when would you usually recommend treatment with LT4? (check all that apply).			
2.5 > TSH \geq 0.6 mU/L and positive thyroid antibodies	15 (7.3)	12 (9.3)	0.539
4 > TSH \geq 2.5 mU/L and negative thyroid antibodies	97 (46.9)	61 (47.3)	1.000
4 > TSH \geq 2.5 mU/L and positive thyroid antibodies	160 (77.3)	105 (81.4)	0.491
10 mU/L > TSH \geq 4 mU/L	184 (88.9)	103 (79.8)	0.024
TSH \geq 10 mU/L	189 (91.3)	110 (85.3)	0.070
Low FT4 with normal TSH	55 (26.6)	45 (34.9)	0.143
A case-by-case basis, taking into consideration the history of infertility treatment, miscarriage, and other factors	133 (64.3)	74 (57.4)	0.249

*. The data on certified specialists are taken from ref. 13.

**, Bolds indicate statistical significances.

LT4 combination therapy for patients with persistent symptoms despite normalized TSH. In contrast, non-certified members largely rejected LT3 use, adhering to old guidelines from ATA and ETA stating that LT4 monotherapy is

sufficient [5, 6]. This suggests that certified specialists, who are exposed to more complex cases and emerging debates during their longer period of medical practice as thyroid specialists, apply guidelines with greater nuance, whereas

non-certified members follow a strict interpretation. Such conservatism may reduce the risk of inappropriate therapy but could result in undertreatment for patients who might benefit from carefully monitored combination therapy. Similarly, European endocrinologists were more likely to use LT3 + LT4 combination therapy than non-endocrinologists [17].

Preference for LT3 + LT4 combination therapy by experienced certified specialists, that is those who were >60 years old and those with >30 year-experience in clinical practice, in our previous study [22] and association of combination therapy with high volume clinical practice in non-certified members (>100 hypothyroid patients per year) in this study, suggest that long clinical experience and high volume practice with hypothyroid patients are associated with a tendency to use LT3 + LT4 combination treatment.

However, both certified specialists and non-certified member groups similarly recognized that persistent symptoms in biochemically euthyroid patients on LT4 are mainly due to “psychological factors,” “comorbidities,” or “unrealistic expectations” rather than “inability of levothyroxine to restore tissue euthyroidism.” Thus, a small but notable proportion of respondents (certified specialists and fewer non-certified members) would prescribe combination therapy in such cases, although they consider that most of these hypothyroid-like symptoms are nonthyroidal. The underlying reasons for this dissonance are thought to be attributable to several factors, including personal, unsubstantiated endorsement of LT3 + LT4 combination therapy, patient requests, and frequent exposure to complex cases. Of interest, this finding is observed in all published THESIS surveys [17-21], suggesting that it is not influenced by geographical or cultural factors. Somatization, type D-personality and medically not yet explained symptoms have been highlighted as important potential contributors of unexplained hypothyroid-like symptoms in patients on LT4 [8-10].

Important differences were also observed in the management of euthyroid patients. Compared to certified specialists, non-certified members were more likely to reject TH use for euthyroid patients. From a patient-safety perspective, the certified specialist approach risks overtreatment and potential iatrogenic thyrotoxicosis, while the non-certified members approach may prevent unnecessary exposure but could overlook potential—albeit unproven—benefits. However, again, since the higher rate of TH prescription was seen in non-certified members who see >100 hypothyroid patients per year than those seeing <100 patients, similar underlying causes mentioned in combination therapy may be considered. In contrast, more non-endocrinologists than endocrinologists considered hypercholesterolemia, simple goiter and obesity to

be a potential indication for TH treatment in Europe [13, 14, 16], data interpreted as indicating that “more experienced prescribers of TH may have a greater awareness of the limitations and side effects of this treatment.” The reasons for this discrepancy are at present unknown.

The above-mentioned findings highlight the influence of physician training and practice environment. Certified specialists working in thyroid-focused settings encounter a high volume of patients with unresolved complaints and complex clinical presentations, which may foster a willingness to explore non-standard treatments. Non-certified members, who manage hypothyroidism as one part of a broad general practice, appear to rely more strictly on guidelines and avoid deviations. While this dichotomy reflects different professional roles, it also creates variability in patient care depending on type of physician consulted.

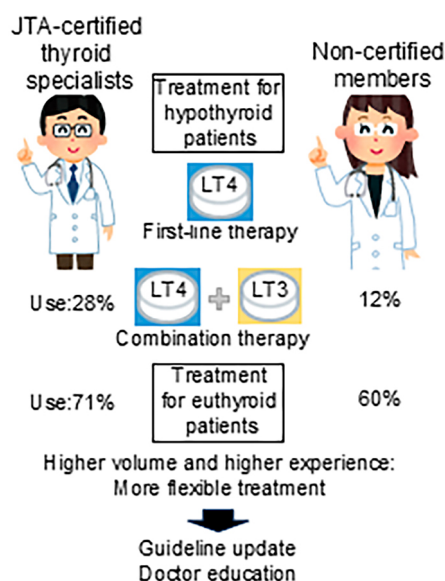
To minimize such variability, several measures are needed. First, the development of updated, Japan-specific guidelines on hypothyroidism management is warranted. National recommendations could clarify when, if ever, combination therapy should be considered and explicitly address the inadvisability of TH use in euthyroid individuals. Second, targeted continuing medical education is essential. For example, not only non-certified members but also certified specialists appear to lack training in how to address persistent hypothyroid-like symptoms [8].

The low response rate from non-certified members compared to that from certified specialists is a limitation of this study. Another limitation is that data on non-certified members may not necessarily represent those on general physicians in Japan, because of their certain levels of interest and/or involvement in thyroid care. Furthermore, non-certified members may refer complex cases to certified specialists rather than manage them independently, which could have influenced the survey results.

In conclusion, this study reveals both shared practices and important differences in TH prescribing between JTA-certified thyroid specialists and non-certified members in Japan (Graphical Abstract). While certified specialists show greater flexibility and individualized approaches which carry risks of overtreatment, non-certified members adhere more rigidly to guidelines. Updating national guidelines, strengthening physician education, and promoting a balance between evidence and individualized care will be crucial to ensure that all patients receive safe and effective management of thyroid disorders.

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Graphical Abstract

Disclosure

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Author Contributions

Conceptualization, methodology, project administration and supervision: R.A., E.P., P.P, E.V.N., L.H., K.I. and H.Y. Data collection and curation, visualization and writing of the original draft: Y.N., J.T., T.M., N.W., S.S., H.S. and S.T. Formal analysis and visualization: Y.N., S.S., H.S. and S.T. Review and editing: R.A., E.P., P.P, E.V.N., L.H., K.I. and H.Y.

References

- Watanabe N (2025) A narrative review of long-term inorganic iodine monotherapy for Graves' disease with a historical relationship between iodine and thyroid. *Endocr J* 72: 23–36.
- Hegedüs L, Bianco AC, Jonklaas J, Pearce SH, Weetman AP, *et al.* (2022) Primary hypothyroidism and quality of life. *Nat Rev Endocrinol* 18: 230–242.
- Bianco AC (2024) Emerging therapies in hypothyroidism. *Annu Rev Med* 75: 307–319.
- Lan H, Wen J, Mao Y, Huang H, Chen G, *et al.* (2022) Combined T4 + T3 therapy *versus* T4 monotherapy effect on psychological health in hypothyroidism: a systematic review and meta-analysis. *Clin Endocrinol (Oxf)* 97: 13–25.
- Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, *et al.* (2014) Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. *Thyroid* 24: 1670–1751.
- Pearce SH, Brabant G, Duntas LH, Monzani F, Peeters RP, *et al.* (2013) 2013 ETA Guideline: management of subclinical hypothyroidism. *Eur Thyroid J* 2: 215–228.
- Jonklaas J, Bianco AC, Cappola AR, Celi FS, Fliers E, *et al.* (2021) Evidence-based use of levothyroxine/liothyronine combinations in treating hypothyroidism: a consensus document. *Thyroid* 31: 156–182.
- Hegedüs L, Van Der Feltz-Cornelis CM, Papini E, Nagy EV, Weetman AP, *et al.* (2024) Medically not yet explained symptoms in hypothyroidism. *Nat Rev Endocrinol* 20: 685–693.
- Perros P, Nagy EV, Papini E, Van Der Feltz-Cornelis CM, Weetman AP, *et al.* (2023) Hypothyroidism and somatization: results from E-Mode patient self-assessment of thyroid therapy, a cross-sectional, international online patient survey. *Thyroid* 33: 927–939.
- Perros P, Nagy EV, Papini E, Abad-Madroñero J, Lakwijk P, *et al.* (2024) Hypothyroidism and type D personality: results from E-MPATHY, a cross-sectional international online patient survey. *J Clin Endocrinol Metab* 110: e97–e108.
- Hegedüs L, Nagy EV, Papini E, Perros P (2025) Limiting the use and misuse of liothyronine in hypothyroidism. *Nat Rev Endocrinol* 21: 3–4.
- Ettleson MD, Ibarra S, Wan W, Peterson S, Laiteerapong N, *et al.* (2023) Demographic, healthcare access, and dietary factors associated with thyroid hormone treatments for hypothyroidism. *J Clin Endocrinol Metab* 108: e1614–e1623.
- Galofré JC, Díez JJ, Attanasio R, Nagy EV, Bednarczuk T, *et al.* (2025) Thyroid hormone treatment for hypercholesterolemia in euthyroid patients: results from a European survey of thyroid specialists. *Clin Endocrinol (Oxf)* 103: 749–756.
- Papini E, Attanasio R, Žarković M, Nagy EV, Negro R, *et al.* (2025) Thyroid hormones for euthyroid patients with simple goiter growing over time: a survey of European thyroid specialists. *Endocrine* 87: 262–272.
- Negro R, Žarković M, Attanasio R, Hegedüs L, Nagy EV, *et al.* (2024) Use of levothyroxine for euthyroid, thyroid antibody positive women with infertility: analyses of aggregate data from a survey of European thyroid specialists (treatment of hypothyroidism in Europe by specialists: an international survey). *Clin Endocrinol (Oxf)* 101: 180–190.

16. Galofré JC, Díez JJ, Attanasio R, Nagy EV, Negro R, *et al.* (2025) Treatment of obesity with thyroid hormones in Europe. Data from the THESIS* Collaboration. *J Endocrinol Invest* 48: 201–212.
17. Attanasio R, Žarković M, Papini E, Nagy EV, Negro R, *et al.* (2024) Patients' persistent symptoms, clinician demographics, and geo-economic factors are associated with choice of therapy for hypothyroidism by European thyroid specialists: The "THESIS" collaboration. *Thyroid* 34: 429–441.
18. Lafontaine N, Brown SJ, Perros P, Papini E, Nagy EV, *et al.* (2024) Use of thyroid hormones in hypothyroid and euthyroid patients: A survey of members of the Endocrine Society of Australia. *Clin Endocrinol (Oxf)* 100: 477–485.
19. Casemiro JF, Ilera V, Batalles S, Reyes A, Nagy EV, *et al.* (2023) Use of thyroid hormones in hypothyroid and euthyroid patients: a 2022 THESIS questionnaire survey of members of the Latin American Thyroid Society (LATS). *Thyroid Res* 16: 40.
20. Liu A, Morrison D, Hegedüs L, Nagy EV, Papini E, *et al.* (2025) Canadian endocrinologists' perspectives on treatment with thyroid hormone substitutions in euthyroid and hypothyroid patients: a 2023 THESIS questionnaire survey. *Clin Endocrinol (Oxf)* 103: 739–748.
21. Sasson L, Kaminer K, Cohen CA, Hegedüs L, Negro R, *et al.* (2025) Thyroid hormone use in clinical practice by Israeli endocrinologists: a THESIS* questionnaire survey : *Treatment of hypothyroidism in Europe by specialists: an international survey. *Thyroid Res* 18: 12.
22. Nagayama Y, Tajiri J, Murakami T, Watanabe N, Sato S, *et al.* (2025) A questionnaire survey of thyroid specialists in Japan on the use of thyroid hormones in hypothyroid and euthyroid patients. *Endocr J* 72: 911–923.
23. Kanda Y (2013) Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant* 48: 452–458.