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ORIGINAL

A questionnaire survey of thyroid specialists in Japan on the use of thyroid hormones in hypothyroid and euthyroid patients

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Abstract. Levothyroxine (LT4) is the established treatment for hypothyroidism but some controversies, such as whether combining it with liothyronine (LT3) for hypothyroid patients and whether prescribing it to euthyroid patients, exist on its use. This survey was conducted to investigate current trends about thyroid hormone use in hypothyroid and euthyroid patients in Japan. Members of the Japan Thyroid Association (JTA) were invited to participate in an online questionnaire based on the THESIS (Treatment of Hypothyroidism in Europe by Specialists: An International Survey) survey. Anonymous responses from 207 of 874 (23.7%) JTA-certified thyroid specialists were analyzed. LT4 was the first line treatment for hypothyroidism by all respondents. 18.8% and 28.0% would also use LT3 and LT3 + LT4 combination, respectively. LT3 + LT4 combination was preferred for patients on LT4 with residual symptoms or low serum T3 levels. Psychological factors and comorbidities were considered as the main contributors to residual symptoms. Respondents would prescribe thyroid hormones in euthyroid subjects for female infertility with positive anti-thyroid antibodies (46.9%), for Hashimoto's disease with a huge goiter (29.0%), and for pregnant or infertile women with TSH between 2.5–4 mU/L irrespective of anti-thyroid antibody status (43.0 and 76.8%, and 46.9 and 77.3%, respectively). In conclusion, Japanese thyroid specialists chose LT4 as first line treatment for hypothyroidism in accordance with current guidelines. The use of LT3 + LT4 combination is less frequent in Japan than in other countries, whereas the use of thyroid hormones for non-hypothyroid indications is similarly high worldwide, which is not necessarily in accord with pertinent society guidelines.

Key words: THESIS questionnaire, Thyroid hormones, Hypothyroidism, Levothyroxine, Liothyronine

Introduction

Primary hypothyroidism is a common endocrine disorder with a prevalence of 0.6–12.0% in women and 1.3–4.0% in men [1]. In Japan, an iodine-sufficient country, its most common cause is Hashimoto's disease [2]. The first-line treatment for hypothyroidism is lifelong replacement therapy with levothyroxine (LT4) with the aim of normalization of serum TSH levels, symptom resolution, and improvement of quality of life [3].

Despite achieving biochemical euthyroidism (normal serum TSH levels) following LT4 administration, 10 to 20% hypothyroid patients complain of persistent hypothyroidism-like symptoms [4, 5] and are dissatisfied with LT4 treatment [6]. The benefit of adding LT3 to LT4 (*i.e.*, LT3 + LT4 combination therapy) has long been

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proposed, but the superiority of LT3 + LT4 combination therapy or desiccated thyroid extract (DTE, containing both T3 and T4) compared with LT4 monotherapy has never been convincingly confirmed [7]. Reasons for persistent symptoms and dissatisfaction, such as somatization [8] and type D personality [9], have only recently become targets of investigation, but many symptoms remain unexplained [4]. However, by targeting only LT4-treated symptomatic patients, recent studies argue that such patients may benefit from LT3 + LT4 or DTE [10, 11]. A recent consensus statement has concluded that patients on LT4 with persistent symptoms may warrant a trial of LT3 + LT4 combination therapy [12]. Whether based on the aforementioned or not, the number of patients offered combination therapy has increased in some countries where LT3 is available [13] and has doubled in the last 10 years in the USA [14].

In Japan, there are no guidelines for the treatment of hypothyroidism and the Japan Thyroid Association (JTA) recommends following the guidelines published by the American Thyroid Association (ATA) [3] and the European Thyroid Association (ETA) [15], both of which are more than a decade old.

Importantly, thyroid hormones (TH) are also prescribed to patients with normal thyroid function, for reasons that are not entirely clear or based on evidence [4].

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 [13]. This survey was initiated in 28 European countries in 2019, many of which have reported their findings [13, 16-36]. Subsequently, the survey was conducted in Australia [37] and by the Latin American Thyroid Society (LATS) [38]. As these surveys have revealed controversial trends in the use of TH for hypothyroid and euthyroid patients, we performed this survey in Japan to evaluate the use of TH by Japanese thyroid specialists and to compare results with those obtained in other countries.

Materials and Methods

The questionnaire survey

We used the THESIS questionnaire [13], amended to fit the Japanese clinical setting by deleting 13 questions from the original version, adding two questions from the modified version of Australia [37] and creating five questions and three options unique to Japan. The survey consisted of 10 demographic questions (questions A1 to A10) and 15 questions on the respondents' approach to TH use in hypothyroid and euthyroid individuals (questions B1 to B15) (Supplementary Table 1). The questionnaire was translated from English into Japanese. All members of JTA were invited to anonymously participate in an online questionnaire with *Google Forms*®, a free-access platform, in 2024 with no reminder circulated. Completion of the survey took approximately 10 minutes. Repeat submissions using the same IP address were automatically blocked.

The JTA has certification systems for thyroid specialist doctors and thyroid specialty facilities. 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 thyroid specialty facilities accredited by the JTA; (i) Have JTA-certified thyroid specialists on staff; (ii) Provide sufficient outpatient thyroid care; and (iii) Can carry out the laboratory tests necessary for thyroid care.

Although the questionnaire was sent to all the member of the JTA (2,938), only the responses from JTA-certified thyroid specialists were summarized in this study.

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 analysis used Chi-squared test, Fisher's exact test and logistic regression analysis to assess the associations between responses to each question and demographic variables. All covariates with a $p < 0.15$ in a univariate analysis were introduced into a multivariate model. 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) [39], which is a graphical user interface for R version 4.02 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Response rate and respondents' characteristics

The response rate was 23.9% (209/874) of the JTA-certified thyroid specialists, of whom 207 (23.7%) provided consent to participate and completed all demographic questions. The responses to the questions A1 to 10 (the demographic data) and to the questions B1 to 15 are summarized in Tables 1 and 2, respectively.

Table 1 Demographic characteristics of respondents

	# of respondents	(%)
Total	207	(100)
A1. Age		
24–30	0	(0)
31–40	13	(6.3)
41–50	63	(30.4)
51–60	66	(31.9)
61–70	44	(21.3)
>70	21	(10.1)
A2. Gender		
Male	157	(75.8)
Female	49	(23.7)
Unknown	1	(0.5)
A3. Years in medical practice		
1–10	1	(0.5)
11–20	45	(21.7)
21–30	78	(37.7)
31–40	50	(24.2)
>40	33	(15.9)
A4. Specialty (domestic conferences) (check all that apply)		
Endocrinology	173	(83.6)
Internal medicine	55	(26.6)
Pediatrics	3	(1.4)
Pediatric endocrinology	6	(2.9)
Nuclear medicine	2	(1.0)
Surgery	33	(15.9)
Obstetrics and gynecology	0	(0)
Otolaryngology	9	(4.3)
Others	11	(5.3)
Internist*	167	(80.7)
Surgeon[#]	40	(19.3)
A5. Membership (domestic conferences) (check all that apply)		
Endocrine society	168	(81.2)
Endocrine surgery	43	(20.8)
Pediatric endocrinology	8	(3.9)
Otorhinolaryngology head and neck surgery	11	(5.3)
Nuclear medicine	7	(3.4)
Others	39	(18.8)
A6. Where do you practice? (check all that apply)		
University hospital	56	(27.1)
General hospital	76	(36.7)
Thyroid–specific hospital/clinic	73	(35.3)
General clinic	30	(14.5)
Basic research	2	(1.0)
A7. Do you work in a specialty facility accredited by the JTA?		
Yes	144	(69.6)
No	63	(30.4)
A8. Do you treat thyroid patients on a regular basis (daily or weekly)?		
Yes, daily	143	(69.1)
Yes, weekly	62	(30.0)
No, rarely	2	(1.0)
A9. Do you treat patients with hypothyroidism?		
Yes, 10–50 patients	44	(21.3)
Yes, 51–100	32	(15.5)
Yes, >100	119	(57.5)
No, rarely	2	(1.0)
A10. Are you a thyroid specialist certified by the JTA?		
Yes	207	(100.0)
No	0	(0.0)

* Those specialized in endocrinology, internal medicine, pediatrics, pediatric endocrinology and nuclear medicine.
[#] Those specialized in surgery and otolaryngology.

Table 2 Summary of responses to the questionnaire

	# of respondents (%)	
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)
Obesity resistant to life–style interventions	1	(0.5)
Severe hypercholesterolemia, as a complementary treatment	2	(1.0)
Depression resistant to anti–depressant medications	3	(1.4)
Female infertility with high level of thyroid antibodies	97	(46.9)
Simple goiter growing over time	38	(18.4)
Unexplained fatigue	6	(2.9)
Hashimoto's thyroiditis with a huge goiter	60	(29.0)
Differentiated thyroid cancer on active surveillance	37	(17.9)
Differentiated thyroid cancer that cannot be operated on for various reasons	34	(16.4)
B2. Which thyroid hormones should be the first choice for the treatment of hypothyroid patients?		
LT4 tablet	205	(99.0)
LT4 powder	2	(1.0)
LT3 tablet	0	(0)
LT3 + LT4 combination	0	(0)
B3. Which of the following drugs are you prescribing in clinical practice? (check all that apply)		
LT4 tablet	207	(100)
LT4 powder	91	(44.0)
LT3 tablet	39	(18.8)
LT3 + LT4 combination	58	(28.0)
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)
Increase LT4	21	(10.1)
LT3 + LT4 combination	3	(1.5)
LT3 monotherapy	1	(0.5)
B5. Which of the following would you prescribe for a patient established on LT4 who continues to have symptoms?		
No change	146	(70.5)
Increase LT4	42	(20.3)
LT3 + LT4 combination	18	(8.7)
LT3 monotherapy	1	(0.5)
B6. After the start of LT4 replacement therapy, when would you re–check serum TSH?		
After 2 weeks	13	(6.3)
After 4 to 6 weeks	132	(63.8)
After 8 weeks	21	(10.1)
No, I mostly rely on clinical evaluation	41	(19.8)
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)
In subclinical hypothyroidism	2	(1.0)
At the patient's request or as a complementary treatment	4	(1.9)
No, dietary supplements should never be used	200	(96.6)
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)
For a short period, in patients recovering from protracted hypothyroidism	19	(9.2)
In patients with normal serum TSH who still complain of symptoms suggestive of hypothyroidism	41	(15.2)
In hypothyroid patients with normal serum TSH who complain of unexplained weight gain	0	(0)
In patients with normal TSH who have abnormal blood tests (*e.g.*, hypercholesterolemia)	5	(2.4)
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)
6 to 10%	40	(19.3)
11 to 30%	17	(8.2)
>30%	1	(0.5)
Not sure	27	(13.0)

Table 2 Cont.

B10. In your experience what has been the trend over the past 5 years?

I am seeing more such cases	13	(6.2)
I am seeing fewer such cases	1	(0.5)
No change	125	(60.4)
Not sure	68	(32.9)

B11. In most patients treated with levothyroxine who achieve normal serum TSH, persistent symptoms are due to: (select an answer for each)

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
Inability of levothyroxine to restore normal physiology	9 (4.3)	30 (14.5)	94 (45.4)	66 (31.9)	6 (2.9)
Psychological factors	1 (0.5)	7 (3.4)	64 (30.9)	123 (59.4)	12 (5.8)
Comorbidities	2 (1.0)	10 (4.8)	83 (40.1)	105 (50.7)	4 (1.9)
Chronic fatigue syndrome	3 (1.4)	10 (4.8)	89 (43.0)	104 (50.2)	1 (0.5)
Patient unrealistic expectation	2 (1.0)	22 (10.2)	96 (48.4)	80 (38.6)	7 (3.4)
Presence of underlying inflammation due to autoimmunity	4 (1.9)	29 (14.0)	112 (54.1)	62 (30.0)	0 (0)
The burden of chronic disease	4 (1.9)	23 (11.1)	103 (49.8)	75 (36.2)	2 (1.0)
The burden of having to take medication	6 (2.9)	32 (15.5)	104 (50.2)	62 (30.0)	3 (1.4)

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)

	Strongly disagree	Disagree	Neutral	Agree	Strongly agree
Such patients have low tissue T3 levels, despite normal serum TSH and require high doses of thyroid hormones to restore normal health	3 (1.4)	17 (8.2)	51 (24.6)	120 (58.0)	16 (7.7)
The significant improvement is a placebo effect	3 (1.4)	28 (13.5)	114 (55.1)	58 (28.1)	4 (1.9)
High doses of thyroid hormones are euphoric for some patients	5 (2.4)	42 (20.3)	101 (48.8)	55 (26.6)	4 (1.9)
The improvement in symptoms is usually because the high doses of thyroid hormones help patients lose weight	4 (1.9)	60 (29.0)	111 (53.6)	32 (15.5)	0 (0)

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)
Increase LT4 to increase serum FT3 to the extent that the TSH value remains within the reference value	88	(42.5)
Increase LT4 until FT3 normalizes, regardless of the TSH level.	34	(16.4)
Change to LT3	2	(1.0)
LT3 + LT4 combination	13	(6.2)

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 ≥ 2.5 mU/L and negative thyroid antibodies	89	(43.0)
4 > TSH ≥ 2.5 mU/L and positive thyroid antibodies	159	(76.8)
10 mU/L > TSH ≥ 4 mU/L	171	(82.6)
TSH ≥ 10 mU/L	184	(88.9)
Low FT4 with normal TSH	52	(25.1)
A case–by–case basis, taking into consideration the history of infertility treatment, miscarriage, and other factors	135	(72.5)

B15. In a woman who wants to conceive, when would you usually recommend treatment with LT4? (check all that apply).

2.5 > TSH ≥ 0.6 mU/L and positive thyroid antibodies	15	(7.3)
4 > TSH ≥ 2.5 mU/L and negative thyroid antibodies	97	(46.9)
4 > TSH ≥ 2.5 mU/L and positive thyroid antibodies	160	(77.3)
10 mU/L > TSH ≥ 4 mU/L	184	(88.9)
TSH ≥ 10 mU/L	189	(91.3)
Low FT4 with normal TSH	55	(26.6)
A case–by–case basis, taking into consideration the history of infertility treatment, miscarriage, and other factors	133	(64.3)

Use of thyroid hormones for patients with hypothyroidism

At the time of the survey, two brands of LT4 (tablet and powder) and one brand of LT3 tablet were licensed in Japan. No formulation of soft-gel capsules, LT4 liquid solution or DTE were available.

Almost all respondents (99.0%) chose LT4 tablets as the initial treatment for patients with hypothyroidism, and the remaining 1.0% favored LT4 powder. In clinical practice, 18.8% and 28.0% also used LT3 and LT3 + LT4 combination, respectively. Subgroup analysis shows that LT4 powder is preferred by internists over surgeons (p = 0.01, odds ratio (OR) 2.60, 95% confidence interval (95% CI) 1.22–5.52). Among the internists, the respondents whose specialty was pediatrics and/or pediatric endocrinology used LT4 powder more frequently than those of adult endocrinology and/or internal medicine (13/15 *vs.* 107/260, $p < 0.01$).

The intervals between the initiation of LT4 treatment and TSH check was 4 to 6 weeks for the majority of respondents (63.8%), 8 weeks for 10.1% and 2 weeks for 6.3%. Supplements such as iodine and selenium were offered upon patients' request by 1.9%.

Putative causes of persistent symptoms

The majority of respondents (78.7%) estimated that the prevalence of patients with persistent hypothyroidism-like symptoms despite normal serum TSH levels on LT4 treatment was ≤10% and had been stable during the last five years (60.4%).

"Psychological factors" were considered the most likely cause for persistent symptoms in patients treated with LT4, followed by "comorbidities" (selected as "agree" or "strongly agree" options by 65.2 and 52.6 % of the respondents, respectively) (Fig. 1A). The option "inability of levothyroxine to restore normal physiology" was selected by 34.8%, with 57.9% (33/57) among respondents who chose LT3 + LT4 combination as one of the treatments in clinical practice *vs.* 26.0% (39/150) among those who did not ($p < 0.01$). The clinical improvement with supraphysiological doses of LT4 in patients with persistent symptoms was considered due to low tissue T3 levels by 65.7% ("agree" + "strongly agree") of respondents, to a placebo effect by 30.0% and to euphoric effect of LT4 by 28.5% (Fig. 1B).

The rates of respondents who opted to increase LT4 dose or change LT4 monotherapy to LT3 + LT4 combination therapy for persistent symptoms were higher than for abnormal blood tests (20.3% *vs.* 10.1% and 8.7% *vs.* 1.5%, respectively, both $p < 0.01$) (Fig. 2). There were no correlations between the demographic variables and the choice of drugs.

Choice of LT3 + LT4 combination therapy

The low quality of available evidence for LT3 + LT4 combination in treatment of hypothyroid patients was advocated by 68.6% of respondents. However, 15.2% would use LT3 + LT4 combination for patients with persistent symptoms and 9.2% for patients who are recovering from protracted hypothyroidism, but none for unexplained weight gain. In the multivariate analysis, LT3 + LT4 combination was preferred by respondents

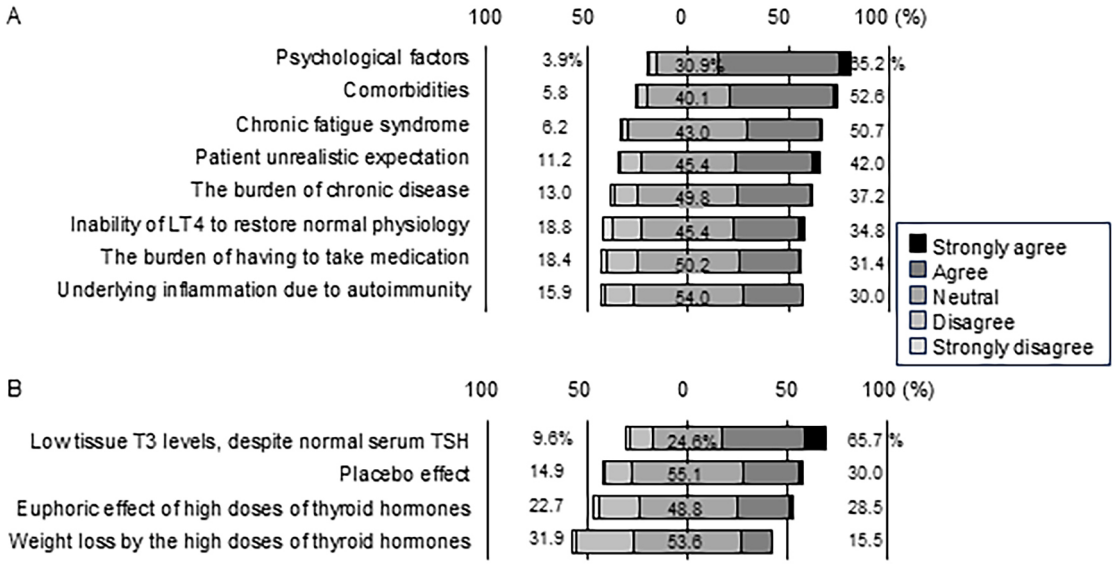


Fig. 1 (A) Opinions regarding the causes of persistent symptoms in patients on LT4 treatment. (B) Opinions regarding the causes of improvement of symptoms in patients treated with supraphysiological doses of thyroid hormones. The numbers on the right, middle and left represent the percentages of "strongly agree plus agree," "neutral" and "disagree plus strongly disagree" options, respectively.

who were older than 60 years (p = 0.02, OR 1.96, 95% CI 1.15–4.09) and with more than 30 years in clinical practice (p = 0.02, OR 2.20, 95% CI 1.06–4.76).

For an athyreotic patient after total thyroidectomy for thyroid cancer, who are ineligible for TSH-suppressive therapy according to present guideline [40] and with subnormal serum FT3 despite normal serum TSH and FT4 levels on LT4 therapy, the majority of respondents preferred LT4 increase (122/207, 58.9%). Most (88/122, 72.1%) would keep TSH levels within the reference range. A minority chose to change LT4 to LT3 alone or to LT3 + LT4 combination (1.0 and 6.2%, respectively).

Use of thyroid hormones for euthyroid patients

As shown in Fig. 3, 29.0% of respondents would never use TH for euthyroid patients, while 46.9% reported using them for female infertility with high titers of anti-thyroid antibodies, 18.4 % for growing simple goiter, and fewer than 3% for other indications (obesity, hypercholesterolemia, depression, or fatigue). With regards to the three additional scenarios included in the Japanese questionnaire, 29.0% selected TH prescription for Hashimoto's disease with a huge goiter, 17.9% for patients with differentiated thyroid cancers on active surveillance and 16.4% for patients with differentiated thyroid cancer that cannot be operated on for various reasons.

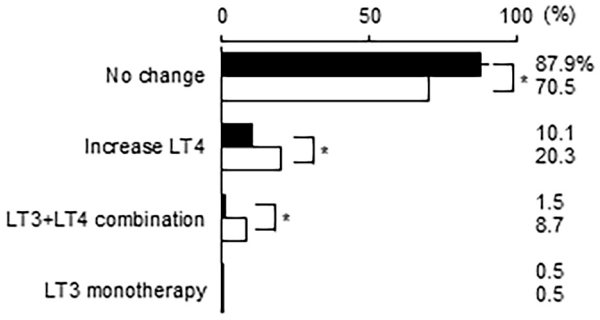


Fig. 2 Percentage of respondents who would use thyroid hormones for euthyroid patients with abnormal blood tests (the solid bars) or with hypothyroidism-like symptoms (the open bars). *, $p < 0.01$.

The multivariate regression analysis revealed that (i) respondents who see thyroid patients daily were more inclined to use TH for euthyroid patients than those who see them weekly ($p < 0.04$, OR 1.95, 95% CI 1.03–3.69); (ii) treatment of a growing simple goiter with TH was preferred by respondents who see more than 50 hypothyroid patients per year compared to those with a lower patient volume (p = 0.02, OR 6.05, 95% CI 1.40–26.2); and (iii) surgeons were more likely than non-surgeons to suggest treatment with TH of inoperable thyroid cancer patients ($p < 0.001$, OR 4.46, 95% CI 2.02–9.89).

Use of thyroid hormones for pregnant or infertile women

A sizeable minority (46.9%) of respondents would consider TH administration in euthyroid females with infertility and high levels of anti-thyroid antibodies (Fig. 2). This was preferred by respondents who were younger than 60 years compared to those who were 60 or more years old ($p < 0.001$, OR 3.46, 95% CI 1.83–6.67).

As shown in Fig. 4A, for a pregnant woman with no special history, 82.6%, 76.8%, 43.0%, and 25.1% of respondents would use TH when (i) 10 mU/L ≥ TSH ≥ 4 mU/L, (ii) 4 > TSH ≥ 2.5 mU/L and positive anti-thyroid antibodies, (iii) 4 > TSH ≥ 2.5 mU/L and negative anti-thyroid antibodies, and (iv) low FT4 with normal TSH, respectively. Similarly, for an infertile woman (Fig. 4B), 77.3%, 46.9%, 7.3%, and 26.6% of respondents would consider treatment with TH when (i) 10 mU/L ≥ TSH ≥ 4 mU/L, (ii) 4 > TSH ≥ 2.5 mU/L

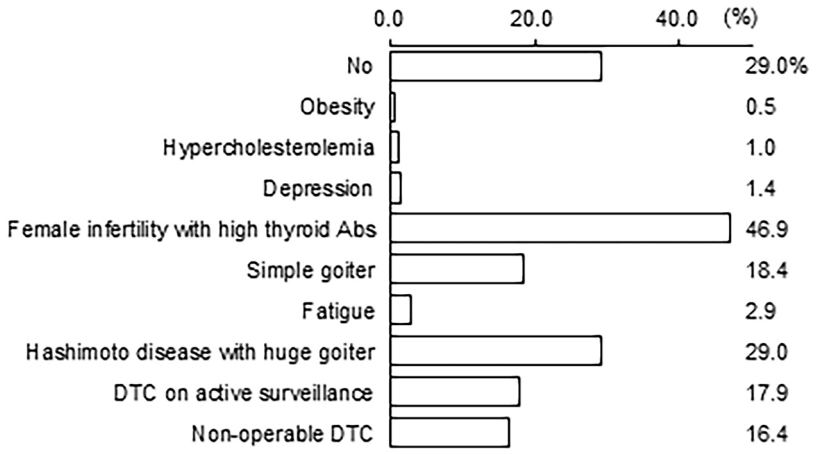


Fig. 3 Percentages of respondents who chose to use thyroid hormones in euthyroid patients with various comorbidities

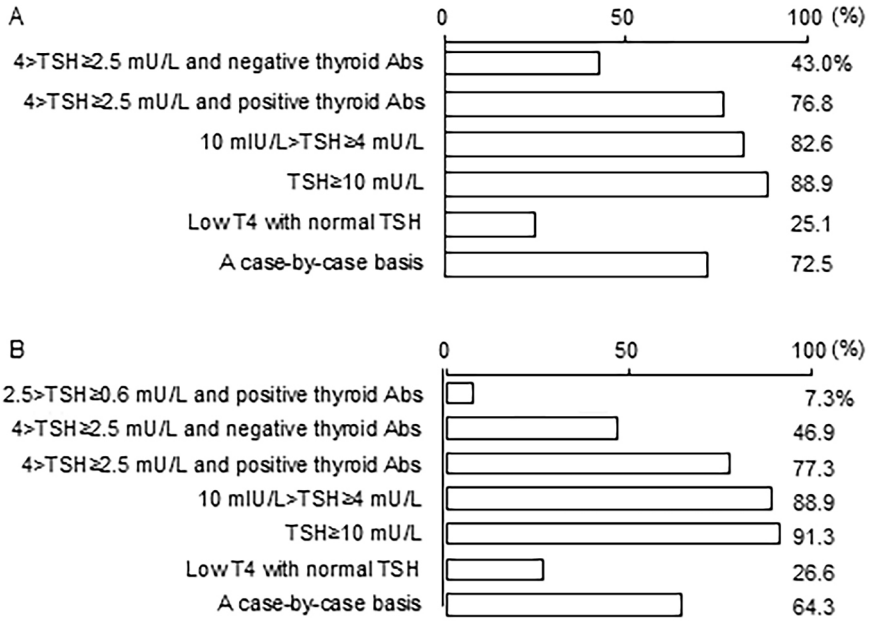


Fig. 4 Percentages of respondents who would prescribe thyroid hormones to (A) a pregnant woman or (B) a woman who wants to conceive

and positive anti-thyroid antibodies, (iii) 4 > TSH ≥ 2.5 mU/L and negative anti-thyroid antibodies, and (iv) low FT4 with normal TSH, respectively. Most respondents (88.9% in both questions) would prescribe TH to a pregnant or infertile subject with TSH >10 mU/L.

The multivariate analyses revealed that respondents >60 years old would not use TH for pregnant or infertile women with 4 > TSH ≥ 2.5 mU/L irrespective of anti-thyroid antibody positivity (p = 0.02, OR 0.48, 95% CI 0.27–0.91; p = 0.03, OR 0.51, 95% CI 0.21–0.87, respectively). The respondents who recommended TH for female infertility also would prescribe them to pregnant or infertile subjects with 4 > TSH ≥ 2.5 mU/L and positive thyroid antibodies (p = 0.02, OR 2.16, 95% CI 1.10–4.87 and p = 0.04, OR 2.63, 95% CI 1.05–7.04, respectively) and to those with 10 > TSH ≥ 2.5 mU/L (p = 0.02, OR 2.18, 95% CI 1.12–5.62 and p = 0.04, OR 2.44, 95% CI 1.11–6.54, respectively). In both cases, >60% (72.5 and 64.3%) of respondents would consider each case individually, taking into consideration the history of infertility treatment, miscarriage and other factors.

Discussion

This first ever survey on clinical use of TH among thyroid specialists in Japan has a response rate of 23.7%, which is lower than in the aggregate European surveys [13] but higher than the Australian and Latin American counterparts [37, 38]. As the JTA members include many non-clinicians, the response rate is most likely underestimated.

Use of thyroid hormones for hypothyroid patients

All respondents used LT4 as the first choice for treatment of hypothyroid patients. The weight-based LT4 prescription to pediatric patients may be a reason for preference of LT4 powder by pediatricians. In Japan, the percentage using LT3 alone or in combination with LT4 (40.6%) is lower than in Australia (54% including DTE) [37] and higher than in Latin America (11.1%) [38]. In Europe its use ranged from 0.9% in Portugal to 58.6% in Denmark [19, 27].

In common with the surveys in Europe, Australia, and Latin America [13, 37, 38], the majority of Japanese respondents found the prevalence of patients with persistent symptoms to be 10% or less, remaining constant over the past five years, and the most likely reasons being “psychological factors” followed by “comorbidities.” The percentage of respondents who supported “presence of underlying inflammation due to autoimmunity” was lowest in Japan (29.2%) and also in many other countries, although it is proposed that persistent symptoms may be related to autoimmune disease itself rather than to hypothyroidism [41].

The supporting rates for “the inability of LT4 to restore normal physiology” hypothesis were similar among Japan (34.8%), Europe (23.6%) and Latin America (28.4%). This rate increased to 57.9% (p < 0.01) in respondents who indicated LT3 + LT4 combination as one of the drugs used in clinical practice, suggesting that respondents willing to use LT3 + LT4 combination therapy for hypothyroid patients may think that LT4 alone cannot be enough to achieve a completely

euthyroid state. A similar pattern was also reported in Poland [26].

Offering the highest percentage, 68.6% of Japanese respondents would never use LT3 + LT4 combination therapy as compared to 42.4% in Europe [lowest in Denmark (11.2%) and highest in Turkey (50.3%)], 29% in Australia and 39.5% in Latin America [13, 19, 31, 37, 38]. Conversely, those who would use LT3 + LT4 combination for hypothyroid patients is lowest in Japan than in the other three surveys. Namely, LT3 + LT4 combination therapy was indicated in patients with residual symptoms by 15.2% in Japan, *vs.* 39.7% in Europe [lowest in Belgium (20%) and the highest in Sweden (78.5%)], 49% in Australia and 48.1% in Latin America [13, 16, 30, 37, 38]. It was also accepted for patients recovering from protracted hypothyroidism by 9.2% in Japan *vs.* 15.7% in Europe [lowest in Denmark (0%) and the highest in Romania (38.8%)], 23% in Australia and 12.3 % in Latin America [13, 19, 28, 37, 38]. The preference for the use of LT3 + LT4 combination therapy by respondents more than 60 years old and with more than 30 years in clinical practice indicates that experienced specialists in Japan likely see many patients on LT4 with residual symptoms and know that LT4 alone is not sufficient to improve symptoms in such patients.

Japanese respondents seemed more inclined to change prescription for a patient on LT4 having residual symptoms than facing abnormal blood tests. Compared to Japan, respondents in Australia preferred to change to LT3 + LT4 combination rather than to increase LT4 dose in a patient with residual symptoms (37 *vs.* 7% in Australia, and 8.7 *vs.* 20.3% in Japan). Nevertheless, the two top ranking causes of persistent symptoms in such a patient are the same in Japan and Australia [37].

Studies have reported lower serum FT3 and higher serum FT4 levels in LT4-treated individuals with normal TSH levels when compared to euthyroid control subjects [42]. Particularly after total thyroidectomy, following radioactive iodine treatment, or in Hashimoto's patients with autoimmune destruction of the thyroid, maintaining serum FT4 levels at the upper limit of reference range is critical to obtain adequate serum FT3 levels due to the absence of T3 secretion by the thyroid [43]. This can be obtained by either increasing LT4 dose or the use of LT3 + LT4 combination therapy, options indicated by 58.9% and 6.2%, respectively, of respondents in Japan. Since the main disadvantage of the use of LT3 is its short half-life, development of slow-release T3 such as T3-sulfate and poly-zinc-T3 may increase the use of LT3 + LT4 combination therapy in Japan [10].

Most respondents in Japan would not use supplements. This is presumably because (i) Japan is an iodine sufficient country, and (ii) selenium decreases thyroid autoantibody levels without clear clinical benefit in Hashimoto's disease [44].

Use of thyroid hormones for euthyroid patients

Japanese respondents' use of TH for euthyroid patients with various conditions was at large similar to that in most other surveys. 29.0% in Japan, 55% in Australia, 43.2% in Latin America and from 9.5% (Czech Republic) to 62.9% (UK) in European countries would not use TH for euthyroid patients [18, 32, 37, 38].

Respondents open to prescribing TH for euthyroid patients were: (i) 18.4% in Japan, 11% in Australia, 12.3% in Latin America and 28% in Europe [lowest in Turkey (6.8%) and the highest in Czech Republic (77.7%)] for growing simple goiter [18, 31, 37, 38], and (ii) less than 10% in many countries for other conditions.

Regarding growing simple goiter, LT4 has long been used empirically with no clear benefit and some non-negligible side effects [45]. Therefore, it is surprising that a sizeable minority of respondents in most countries indicated the use of TH for such patients. The relationships between the proneness to use LT4 for growing simple goiter and respondents' characteristics are different between Europe and Japan. LT4 treatment for growing simple goiter is preferred by older thyroid specialists with long clinical experience in Europe suggesting adherence of older doctors to outdated clinical practice [16, 21]. In Japan, this practice is characteristic of thyroid specialists who see more than 50 hypothyroid patients per year, regardless of age.

Active surveillance is now a widely accepted management option for low-risk papillary thyroid microcarcinoma [46] and TSH suppression by LT4 has long been used widely in post-operative thyroid cancer [47]. A recent work has reported the favorable effect of combination of these two therapeutic options for active surveillance [48]. Considering these reports, LT4 prescription rate for active surveillance could be considered even low. This may be due to an uncertainty about how long TSH suppression, which surely have side effects, should be continued in active surveillance.

Thus, the use of TH for all the scenarios in euthyroid patients, except the last two for thyroid cancer, seems to deviate from evidence-based guidelines.

Use of thyroid hormones for pregnancy and infertility

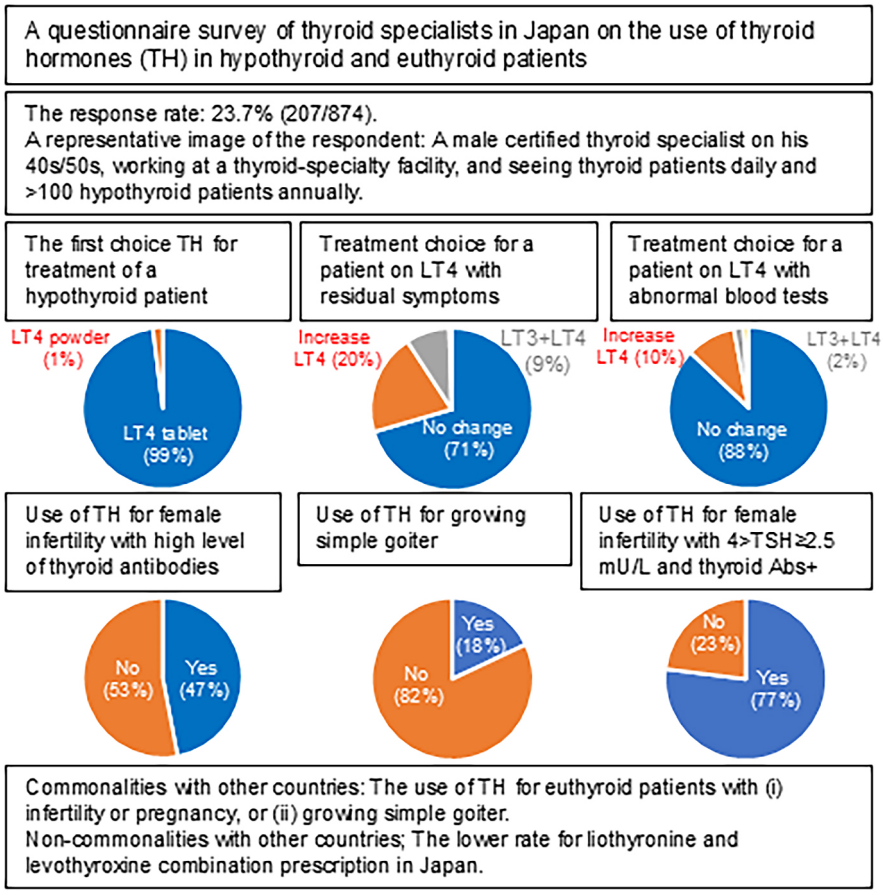
Respondents who indicated TH prescription for female infertility in euthyroid women was similar in the different surveys, namely 46.9% in Japan, 39% in Australia, 46.9% in Latin America and 42.8% in Europe [lowest in Netherland (23%) and the highest in Slovakia (84%)] [37, 38, 49], revealing that this prescription is relatively

common worldwide. Although the 2017 ATA guideline suggested considering daily treatment with LT4 in anti-TPO antibody-positive euthyroid patients to prevent TSH elevation and potentially associated complications [50], the subsequent randomized controlled trials (RCT) and the ETA guidelines do not support this suggestion (see ref. [49] for details). However, the support for using TH is still high in Japan, Australia and Latin America where the surveys were conducted more recently [37, 38]. The fact that the guidelines are not widely followed raises concern about the consequences of overtreatment [49].

Similar concerns also apply to pregnant and infertile subjects. Although ATA guidelines recommend LT4 supplementation to achieve TSH levels <2.5 mU/L in women with subclinical hypothyroidism [50], a recent systematic review with meta-analysis has revealed little benefit from LT4 replacement therapy in pregnant or infertile patients with 2.5 mU/L ≤ TSH < 4.0 mU/L [51]. Although the response options differ slightly between Japan and Australia, the rates of respondents who would administrate LT4 to pregnant patients with 2.5 mU/L ≤ TSH < 4.0 mU/L in Japan and those with TSH above the trimester-specific reference range in Australia are very similar, being 43.0 and 42% in the case of negative thyroid antibodies and 76.8 and 85% in the case of positive anti-thyroid antibodies [37], respectively. The response patterns were also very similar for infertile patients in Japan. Nearly 30% of prescription rates of LT4 to pregnant and infertile subjects with low FT4 and normal TSH are also somewhat surprising, because it is not recommended by ATA guideline [50].

Limitations

As this survey targeted thyroid specialists, not general practitioners, caution should be exercised in generalizing the results. However, since respondents are active in routine management of many hypothyroid patients, the data obtained in this study represent the actual clinical practice by thyroid specialists in Japan and allow a meaningful international comparison. Another limitation is the lack of distinction in this survey between overt and subclinical hypothyroidism and primary and central hypothyroidism in the virtual patient scenarios. Finally, we now think that we should have asked whether serum FT4 and FT3 are measured simultaneously with TSH during TH replacement therapy in hypothyroid and euthyroid patients.



Graphical Abstract

Conclusions

All Japanese thyroid expert respondents use LT4 as the first-line therapy for hypothyroidism (Graphical Abstract). However, a sizable minority of respondents are inclined to use LT3 + LT4 combination therapy for patients on LT4 treatment with hypothyroidism-like symptoms/signs or low serum T3 levels, although nearly one third of them believe that persistence of symptoms is largely due to psychological causes. The rate for LT3 + LT4 prescription in Japan is lower than in other countries, suggesting that thyroid specialists in Japan remain cautious about using this treatment. Future well-designed clinical studies are needed to clarify if LT3 + LT4 combination therapy may have advantages over LT4 monotherapy in a small minority of selected patients [52].

In view of the evidence and the current international guidelines, an unexpectedly high percentage of respondents would use TH for euthyroid patients, especially in case of female infertility with high titers of anti-thyroid antibodies, a growing simple goiter, and Hashimoto's disease with a huge goiter, despite no support from scientific studies or guidelines. This raises concerns about overtreatment with TH, leading to increased comorbidity and mortality. Guidelines for administration of TH to euthyroid patients should be considered in Japan.

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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.

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