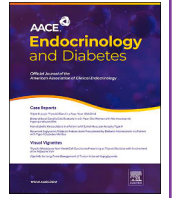




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Original Research

Use of Thyroid Hormones in Patients with Hypothyroidism and Euthyroidism in the United States: American Association of Clinical Endocrinology International Collaboration with the THESIS Investigators

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ABSTRACT

Background/Objective: The management of hypothyroidism has evolved over time as the development of new guidelines and formulations of thyroid hormone have become available.

Methods: A survey of American Association of Clinical Endocrinology members in the United States examining the treatment of hypothyroidism, including questions about initial choice of therapy, use of liothyronine (LT3)-containing regimens, and use of thyroid hormones in hypothyroid and non-hypothyroid patients.

Results: Survey links were opened by 387 of 4000 potential respondents and completed by 299 (7%). Respondents unanimously cited levothyroxine (LT4) as the initial treatment choice for hypothyroidism. Forty-seven percent indicated they would use thyroid hormones in patients with euthyroidism with infertility and elevated thyroid antibodies, with smaller numbers for goiter, depression, hypercholesterolemia, fatigue, and obesity. About 60% would consider combination LT4/LT3 in a patient with euthyroidism who does not feel well on treatment or has persistent symptoms. In contrast, a much smaller minority (16% for LT4/LT3 and 5% for desiccated thyroid extract) used such regimens to manage their own hypothyroidism. Persistent symptoms in treated patients with a normal TSH were most often attributed to psychosocial factors, unrealistic patient expectations, and comorbidities. Significant associations were identified between respondent demographics and treatment choices, most notably age, practice setting, and volume of patients with hypothyroidism. **Conclusions:** LT4 monotherapy is overwhelmingly employed as first line therapy for hypothyroidism by U.S. clinicians. However, the high usage of thyroid hormones for patients whose symptoms were considered to be unrelated to hypothyroidism is at odds with current international guidelines for the management of hypothyroidism.

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Introduction

Hypothyroidism, whether overt or subclinical, is among the most commonly encountered endocrine disorders. While prior estimates of the prevalence of hypothyroidism in the U.S. from 1988 to 1994 using National Health and Nutrition Examination Survey (NHANES) data estimated the figure to be 4.6% of the U.S. population, more recent studies using medical and pharmacy claims data place that figure at 11.7% in 2019.¹

Levothyroxine (LT4) monotherapy is the standard of care for treatment of overt hypothyroidism.^{2–4} Failure to reach treatment targets or persistent physical complaints despite normalization of serum thyrotropin (TSH) levels are common challenges faced by clinicians who care for patients with hypothyroidism.⁵ Liothyronine (LT3) monotherapy and combination LT4-LT3 regimens, including desiccated thyroid extract (DTE), which are not recommended by current guidelines, are also employed.^{2,3} Areas of ongoing study include the association between hypothyroidism and cardiovascular disease, hypothyroidism and obesity/weight management, genetic polymorphisms that lead to an individual set point for therapy, and the effects of hypothyroidism and thyroid antibody positivity on pregnancy outcomes.^{6–17}

In this study, we present the results of a survey of U.S. members of the American Association of Clinical Endocrinology (AACE) on the use of thyroid hormones in hypothyroid and non-hypothyroid patients. Conducted in collaboration with the THESIS (Treatment of Hypothyroidism in Europe by Specialists) investigators, the study is part of a larger research effort examining the management of hypothyroidism around the globe.

Methods

Survey Tool and Aim

A survey was conducted with SurveyMonkey™, an online platform with various tools for data collection. The target population consisted of the 4000 U.S. AACE members who treat patients with hypothyroidism. The aim was to analyze responses in relation to respondent demographics and other characteristics, and to compare them to similar surveys administered around the globe. The questionnaire was initially tested in a pilot study of Italian endocrinologists and subsequently administered in English or other languages in multiple other countries in Europe and Asia. Survey questions were refined to adapt to the U.S. practice setting; however the content was similar to the original questions. The survey consisted of 24 questions, including questions related to the characteristics of the respondents, that required less than 15 minutes to complete (see [Supplementary material](#)).

Study Population

An invitation email that included a link to the survey was sent to the 4000 U.S. AACE members in May and July of 2024, each time followed by a reminder within 2 to 3 weeks aimed at capturing non-respondents. Anonymized responses were stored electronically. As the survey link was not unique to a given respondent, nor were surveys associated with any identifying information, the link could potentially be forwarded to non-members or filled out more than once by the same individual. Participation was anonymous and voluntary; therefore, IRB approval was not required.

Statistical Analysis

Survey results are presented as absolute numbers and percentages of respondents or patients. The statistical analyses were

Highlights

- A survey of the American Association of Clinical Endocrinology members in the United States showed that levothyroxine is the preferred agent prescribed for hypothyroidism, as with similar studies conducted by the Treatment of Hypothyroidism in Europe by Specialists collaborative
- A significant number of clinicians use liothyronine-containing regimens to address persistent symptoms of hypothyroidism, despite a lack of evidence for this intervention
- Thyroid hormone is also prescribed in patients with euthyroidism with infertility and positive antibodies; goiter; and obesity, despite a lack of evidence for benefit
- Choice of therapy is impacted by gender, practice setting and where the clinician received their medical education
- Updated clinical guidance is needed to ensure best practices in the management of hypothyroidism

Clinical Relevance

A study of American Association of Clinical Endocrinology members in the United States examined the management of hypothyroidism. Results were compared to the Treatment of Hypothyroidism in Europe by Specialists collaborative studies conducted around the globe. Initial management of hypothyroidism aligns with clinical guidelines, but other regimens are frequently employed. Thyroid hormone is prescribed to patients with euthyroidism with evidence lacking.

conducted using R software.¹⁸ The survey data were not subjected to weighting. Qualitative variables were reported as frequencies and proportions, whereas quantitative variables were summarized using means and standard deviations. The Chi-square test and Cramer's V test were employed to assess the associations among qualitative variables. Furthermore, logistic and ordinal regressions were performed where appropriate.¹⁹ We performed a multivariable logistic regression analysis with an elastic net for variable selection. Elastic net regularization was chosen to prevent overfitting and address multicollinearity, as it combines the L1 (lasso) and L2 (ridge) penalization methods, shrinking some coefficients toward zero and setting others exactly to zero for variable selection.^{20,21} For analysis of respondent preferences for LT4 formulations in pre-specified clinical scenarios, overall *P* value of less than <0.05 in the clinical groups (columns) was used to compute pairwise differences, with use of Holm's method to adjust *P*-values for multiple comparisons. All analyses were conducted in R (version 4.51, R Foundation for Statistical Computing, Vienna, Austria). Model fitting was performed using the glmnet package,²² with the mixing parameter α and regularization parameter λ jointly tuned by cross-validation. Specifically, we used the `cva.glmnet` function with 20 folds ($n_{\text{folds}} = 20$) to identify the optimal α value (ranging from 0 fully ridge to 1 fully lasso) and corresponding λ that minimized the cross-validated deviance. Associations for the selected predictors are presented as odds ratios (ORs) with 95% confidence intervals from the elastic net-regularized logistic model.

Results

Of the 4000 invitations sent, 387 survey links were opened and 299 completed surveys were submitted; therefore, 7% of eligible

Table 1
Respondent Characteristics

Professional Role	N = 297, (%)
MD/DO Endocrinologist	252 (85)
MD/DO Non-endocrinologist	12 (4)
PA	8 (3)
NP	18 (6)
Fellow in training or resident	7 (2)
Specialty (check all that apply) ^a	N = 298, (%)
Endocrinology	280 (94)
IM	88 (30)
Pediatric Endocrinology	8 (3)
FM	17 (6)
Nuclear Medicine	1 (<1)
GYN/Fertility GYN	2 (<1)
In training	2 (<1)
Other	2 (<1)
Medical education	N = 295 (%)
U.S. medical school or other training program	174 (59)
IMG	121 (41)
Professional Organizations (check all that apply) ^a	N = 291 (%)
AACE	286 (98) ^b
ES	190 (65)
Pediatric ES	3 (1)
ATA	53 (18)
Gender	N = 298 (%)
Female	152 (51)
Male	142 (48)
Non-binary or other	3 (1)
Prefer not to answer	1 (0.3)
Age	N = 296 (%)
20–30	3 (1)
31–40	47 (16)
41–50	67 (23)
51–60	81 (27)
61–70	58 (20)
71–80	37 (13)
>80	3 (1)
Years in clinical practice	N = 295 (%)
0–5	20 (7)
6–10	30 (10)
11–20	76 (26)
21–30	73 (25)
31–40	61 (21)
>40	35 (12)
Practice Setting (check all that apply) ^a	N = 299 (%)
Academic Medical Center	90 (30)
Group practice	89 (30)
Private practice	98 (33)
Government/Military	34 (11)
Health Care Delivery System	22 (7)
Other	14 (5)

ATA = American Thyroid Association; DO = Doctor of Osteopathy; ES = Endocrine Society; FM = family medicine; IM = Internal medicine; GYN = gynecology; IMG = International Medical Graduate; MD = Medical Doctor; NP = nurse practitioner; PA = physician assistant; U.S. = United States.

^a Total numbers of specialties, professional organization memberships and practice settings could exceed the number of respondents as some respondents practice more than one specialty, in more than one setting and may belong to more than one organization.

^b Survey was sent to U.S. AACE members only, although accessing the link did not require a unique log in. Therefore, it could be shared, which likely accounts for the 2% of respondents who were non-members.

respondents and 77% who opened the survey completed it. Some respondents did not answer all questions.

Respondent Characteristics

Respondent characteristics are shown in Table 1. Two hundred ninety-eight respondents indicated how often they treated

patients with hypothyroidism: 85% on a daily basis; 13% on a weekly basis; and 2% rarely. The number of patients that were treated by those respondents per year were: 74% > 100 patients; 15%, 51 to 100 patients; 10%, 10 to 50 patients; and 1%, <10 patients.

For comparison, of the 4000 U.S. AACE members, 3084 listed thyroid disease as an area of interest or expertise. Approximately 1900 of the U.S. Endocrinologist members are in private practice (solo, group, partnerships, etc.), 1000 are in university or hospital settings, 386 have multiple practice settings, and the remaining members work in other settings (eg government, industry). The age distribution of endocrinologist members is as follows: 26% over the age of 56, 21% between the ages of 46 to 55, 22% between the ages of 36 to 45, and 6% below the age of 35. Twenty-five percent did not provide age data. The gender distribution of U.S. endocrinologist members is as follows: 43% female, 55% male, 1% other, or prefer not to answer.

Choice of Thyroid Hormones and Use of Different LT4 Formulations

All (298/298) respondents indicated that LT4 monotherapy is their first choice of treatment for patients with hypothyroidism. While LT4 was overwhelmingly the initial choice of therapy, 65% of those surveyed indicated that they also prescribe LT4 and LT3 in combination, and 35% prescribe DTE.

Fifty-one percent responded that most patients are dispensed the type of LT4 they prescribed, while 33% noted that approval by third party (insurance payers) may be required for their patients to be dispensed the prescribed formulation. Data in Table 2 presents responses regarding the preferred thyroid formulation in various clinical scenarios. In patients with possible gastrointestinal malabsorption or those with good biochemical control but persistent symptoms of hypothyroidism, there were significant differences in preferences for tablets vs liquid and tablets vs soft-gel. For patients taking LT4 correctly with poor biochemical control, there were significant differences in preference for tablets vs liquid and liquid vs soft-gel (see Supplementary material for Supplementary Table 2 statistical analysis).

Monitoring Patients with Hypothyroidism

After the initiation of thyroid hormone, most clinicians (58%) would repeat the serum TSH in 4 to 6 weeks, while 42% would repeat the TSH after 8 weeks. In the case of switching from one manufacturer's formulation to another, 45% of participants would repeat the TSH in 4 to 6 weeks while 44% would wait 8 weeks.

Supplement Use

The use of dietary supplements, such as selenium, in addition to thyroid hormone(s) for patients with hypothyroidism was investigated. Fifty-two percent responded that dietary supplements may be used as complementary therapy or at the patient's request, 26% thought that there was no role for dietary supplements, and 18% indicated a role for dietary supplements in the setting of coexisting autoimmune thyroiditis.

Use of Combination LT4/LT3 and DTE

Several questions explored the use of LT3-containing thyroid hormone regimens, including combination LT4/LT3 and DTE (Fig. 1). Most respondents (59% and 60% respectively), would consider combination LT4/LT3 therapy in patients who had

Table 2
Respondent Preferences for LT4 Formulations in Pre-specified Clinical Scenarios

Formulation	Least Subject to Variable Absorption	Patients with Possible Gastrointestinal Malabsorption	Patient Taking LT4 Correctly with Poor Biochemical Control	Patient with Poor Biochemical Control and who is Unable to take LT4 Correctly	Patient with Good Biochemical Control but Persistent Symptoms of Hypothyroidism
Tablets	19%	44%	37%	22%	30%
Soft-gel capsules	26%	25%	27%	22%	7%
Liquid	26%	18%	10%	22%	4%
No Major Changes with the Different Formulations	29%	13%	26%	34%	59%

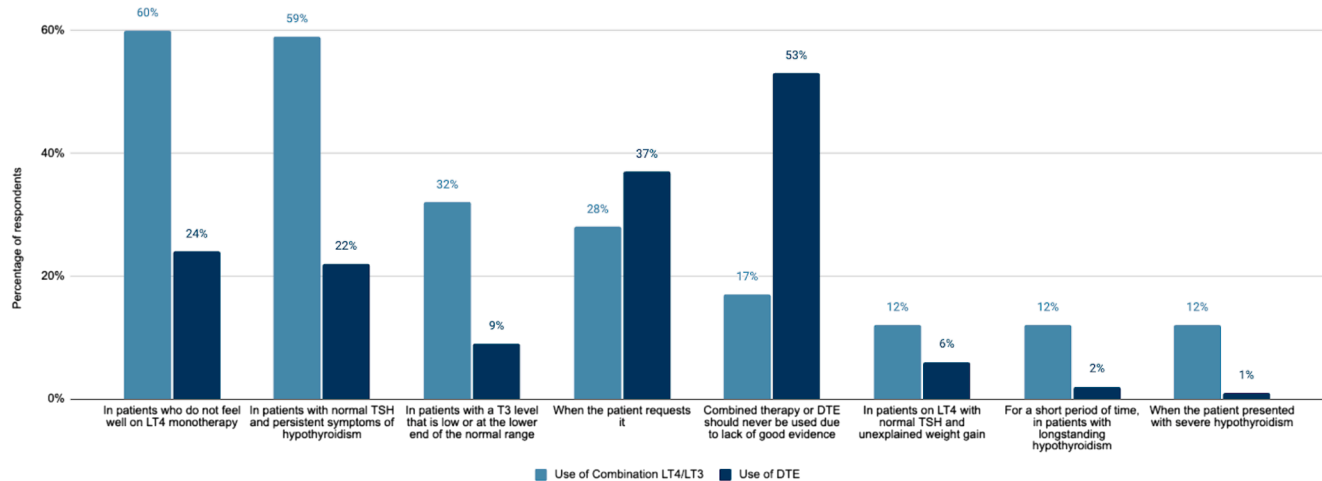


Fig. 1. Use of combination LT4/LT3 and DTE.

Table 3
Respondent Answers Regarding Perceived Prevalence of Persistent Symptoms with Normal TSH and Trends Over Time

How Common is the Phenomenon of Persistent Symptoms in the Setting of Normal TSH? N = 297		In Your Experience, What Has Been the Trend Over the Last 5 y? N = 295	
<5% of patients	63 (21%)	More cases	112 (38%)
6-10%	103 (35%)	Fewer cases	29 (10%)
11-30%	90 (30%)	No change	123 (42%)
>30%	29 (10%)	Not sure	31 (11%)
Not sure	12 (4%)		

persistent symptoms despite a normal TSH or in patients who do not feel well on LT4 monotherapy. However, 17% and 53% respectively, indicated that a combination regimen or DTE should never be used, due to the low quality of available evidence, while 36% indicated that patients treated with DTE experienced more symptoms of thyrotoxicosis than those treated with LT4. Thirty-two percent and 9% would prescribe combination therapy or DTE, respectively, to patients with a low or low-normal serum T3 level. Seventy-five percent and 89% reported that they prescribe combination LT4/LT3 or DTE, respectively, to less than 5% of their patients with hypothyroidism.

Perceived Prevalence, Trends Over Time, and Causes of Persistent Symptoms

The prevalence of patients with persistent symptoms of hypothyroidism despite a normal TSH on LT4 and trend over the last 5 years was assessed (Table 3). Forty-two percent reported no

change, 38% felt there was an increase, while only 10% a decrease. The principal reported bases for ongoing symptoms were psychosocial factors (78%), unrealistic patient expectations (75%), and medical comorbidities (73%) (Fig. 2).

Clinician Responses About Self-Management of Hypothyroidism

Of the 296 practitioners who answered, 41 (14%) reported having a diagnosis of hypothyroidism, 246 (83%) did not, and 9 (3%) preferred not to answer. Eleven (26%) of the 43 individuals who responded to the question reported experiencing excessive fatigue or tiredness and 32 (74%) did not. Figure 3 shows that 16% and 5% of clinicians with hypothyroidism reported having tried combination therapy with LT4/LT3 or DTE, respectively. Of 283 respondents answering the question about whether they would consider either combination LT4/LT3 or DTE for themselves if they developed hypothyroidism, 97 (34%) responded “Yes” and 186 (66%) responded “No.”

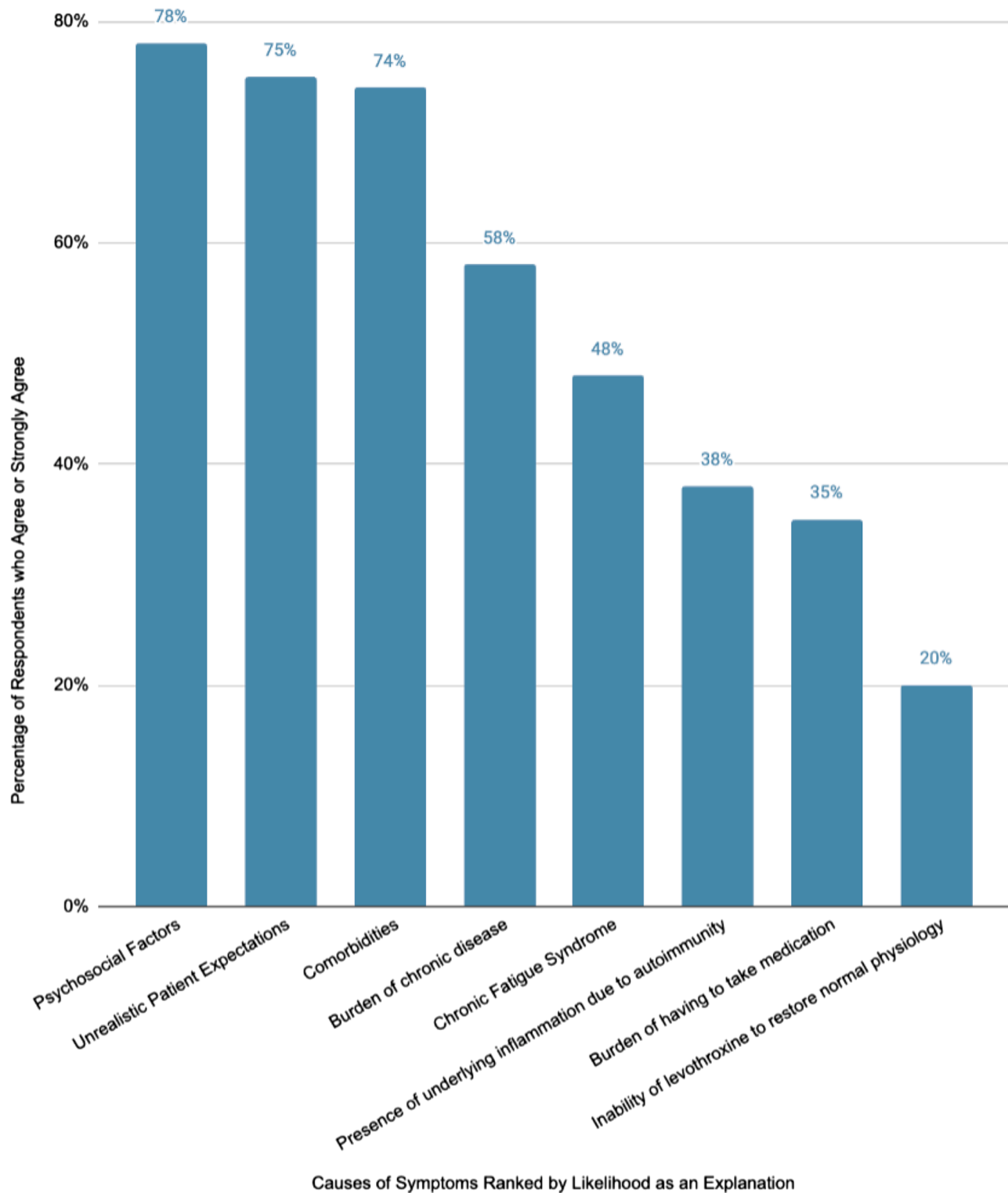


Fig. 2. Causes of persistent symptoms in treated patients with normal TSH.

Use of Thyroid Hormone in non-hypothyroid Patients

Proposed indications for treatment of euthyroid patients are presented in [Figure 4](#). A significant proportion (47%) answered that the use of thyroid hormone may be indicated in the setting of female infertility in a euthyroid patient with elevated thyroid antibodies. An equal proportion (47%) responded that treatment with thyroid hormone is never indicated in euthyroid patients.

Statistical Analysis

Univariate Analysis

Due to very small numbers of respondents, the gender categories of Other, Non-Binary, and Prefer not to Answer were excluded from the analysis. Clinicians over the age of 70 were less likely to prescribe combination LT4/LT3 in the setting of patients not feeling well on LT4 monotherapy (odds ratio [OR]: 0.43; 95% confidence interval (CI)

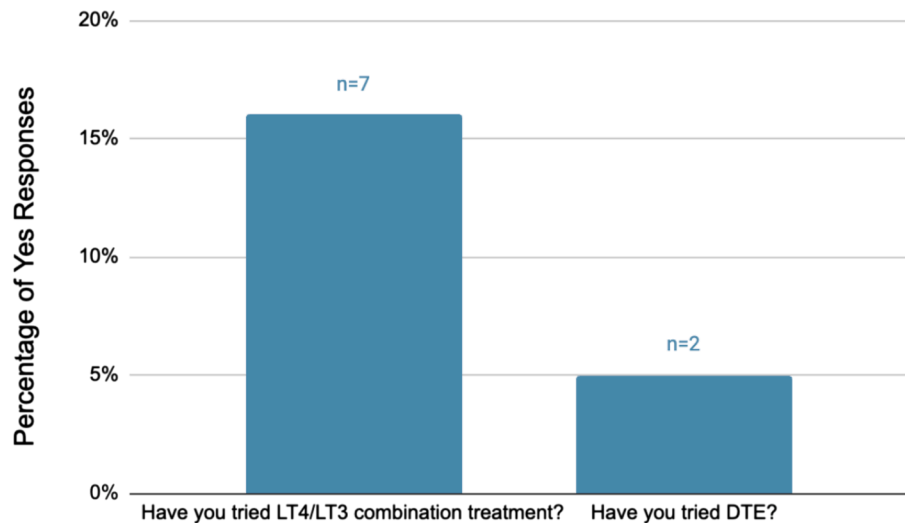


Fig. 3. Use of LT4/LT3 or DTE by clinicians with hypothyroidism.

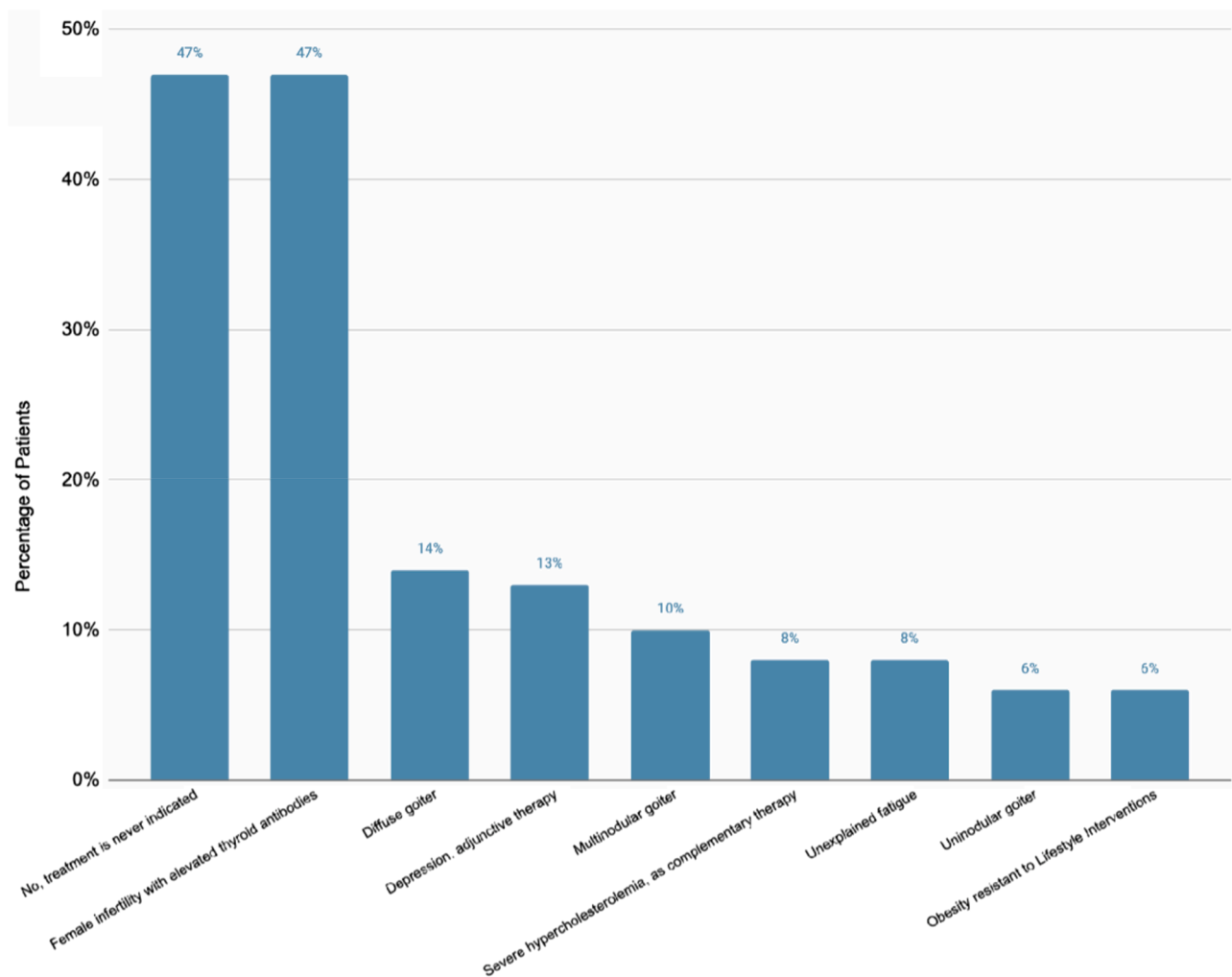


Fig. 4. Thyroid hormones may be indicated in patients with biochemically euthyroidism with (check all that apply).

[0.19-1.02]) and were more likely to respond that combination therapy is never indicated (OR: 3.53 [1.2-10.4]). Those who specialized in endocrinology were more likely to prescribe combination LT4/LT3 therapy to patients with persistent symptoms or who do not feel well on LT4 monotherapy (OR: 3.35 [1.24-9.07] and OR: 3.45 [1.27-9.35], respectively), as well as at the request of the patient (OR: 7.33 [0.96-55.8]). Age >60 (OR: 0.44 [0.20-0.95]) and >70 (OR: 0.17 [0.06-0.44]) were associated with a lower likelihood of prescribing

LT4 in the setting of a euthyroid female patient with infertility. Analysis did not show any significant associations for use of thyroid hormone in diffuse goiter, uninodular or multinodular goiter, due to the small number of positive responses to those questions. See Supplement for complete data set.

Multivariable Analysis

Analysis revealed statistically significant associations for gender, age, practice setting and whether the respondent received their postgraduate education in the U.S. or elsewhere. Data were analyzed both for all subjects and physicians only, the latter not shown, due to minimal differences between the 2 groups. (Table 4; See Supplement for complete data set).

U.S., European, and Western Asia Comparison

For the multivariable statistical analysis, variables that have demonstrated significance in previous THESIS research were employed. Variables used were continent (U.S., Europe, Western Asia), gender, years in medical practice, practice setting, medical specialty, and number of hypothyroid patients treated per year. Table 5 shows a comparison of data from U.S., European, and Western Asia survey responses. The data shows agreement among respondents from the 3 regions about the explanation for persistent symptoms in those with normal TSH values or thyroid hormone treatment in patients euthyroidism with female infertility, hypercholesterolemia and obesity. Differences across the 3 regions were seen in respondent age, years in medical practice, practice setting, control over formulation prescribing, use of dietary supplements, and use of LT4/LT3-containing regimens in both patients with hypothyroidism and self-management of hypothyroidism.

Table 4
Multivariable Analysis for Use of LT4 in Euthyroid Subjects, Use of DTE, Indications for Use of Combination LT4/LT3, and Causes of Persistent Symptoms

Option	Ranked Higher Odds Ratio [95% Confidence Interval]	Ranked Lower Odds Ratio [95% Confidence Interval]
Use of LT4 in patients with euthyroidism		
Fatigue	Males: 2.389 [0.1-5.72]	
Obesity		University center 0.22 [0.05-0.98]
Female infertility	Med. Educ. in US: 1.65 [1.01-2.68]	Group practice 0.22 [0.05-0.99]
		Age 41-50 0.45 [0.21-0.95]
		Age 61-70 0.39 [0.18-0.85]
		Age >70 0.14 [0.05-0.37]
Diffuse goiter	Males: 2.356 [1.19-4.68]	
Uninodular goiter	Private Practice: 4.11 [1.47-11.47]	
Multinodular goiter	Private Practice: 3.74 [1.69-8.29]	
NEVER indicated	Age 41-50: 2.79 [1.31-5.96]	Treat hypothyroidism daily/weekly 0.12 [0.02-0.73]
	Age 61-70: 2.01 [0.93-4.35]	University center: 0.57 [0.34-0.96]
	Age >70: 2.39 [1.01-5.62]	
Use of combination LT4/LT3		
Longstanding hypothyroidism	Male: 3.09 [0.81-11.76]	
	Other practice ^a 3.99 [0.77-20.73]	
When patient not feeling well	Med. Educ. in US: 2.88 [1.74-4.76]	Age>70: 0.28 [0.11-0.69]
		Govt./Military: 0.50 [0.23-1.07]
At the request of the patient	Med. Educ. In US: 2.59 [1.45-4.62]	
	Group Practice: 2.58 [1.42-4.68]	
	University center: 1.78 [0.97-3.28]	
Use of DTE		Med. Educ. In US: 0.46 [0.29-0.74]
NEVER indicated		
Causes of persistent symptoms		
Inflammation	Males: 2.34 [1.49-3.67]	Age >70: 0.66 [0.30-1.42]
	Age 41-50: 1.87 [0.98-3.59]	Treat hypothyroidism Daily/Weekly:
	Med. Educ. In US: 2.27 [1.47-3.49]	0.22 [0.06-0.88]
	Group Practice: 2.29 [1.44-3.63]	

Educ, Education; Govt, Government; Med, Medical.

Blank box indicates no statistically significant results for this option.

^a "Other" practice settings comprised 4.7% of respondents and referred to working in a setting other than academic, private, group, military, or health care delivery system.

Discussion

Endocrinologists comprised 85% of our survey respondents, 51% of whom were female, which is similar to a published national figure (53%).²³ The distribution of years in practice were also similar to other physician surveys on hypothyroidism; 84% practiced for more than 10 years, compared to 81% by Esfandiari et al and 53% by Jonklaas et al.^{24,25} While the survey response rate was low, the absolute number of respondents in our survey (*n* = 299) was similar to other widely cited recent U.S. based surveys of endocrinologists relating to hypothyroidism (*n* = 389 for Jonklaas et al, 2018, *n* = 359 for Esfandiari et al, 2019). Therefore, we believe our findings are likely to reflect how endocrinologists treat hypothyroidism in the U.S.

Choice of Therapy: Levothyroxine Monotherapy vs Liothyronine-Containing Regimens

A subset of patients with hypothyroidism treated with levothyroxine are dissatisfied with their treatment and have impaired quality of life, which may play a role in the use of LT3-containing thyroid regimens.²⁶ Clinical trials, however, have not shown a consistent benefit of treatment with LT4/LT3 or DTE.^{27,28} The basis for persistent symptoms may not be identified for the majority of such patients, and whether this is related to thyroid hormone therapy continues to generate controversy. Recent multinational cross-sectional surveys demonstrate a high prevalence of somatization and type D personality in the subset of patients with hypothyroidism who report negative treatment outcomes, as is the case in patients with other chronic medical conditions.^{29,30} Medically not yet explained symptoms (MNYES) are frequently

Table 5
Comparison of U.S., European, and Western Asia Survey Responses

	U.S.	Europe	Western Asia
Age >60	33%	14%	18%
Years in Medical Practice			
<10	17%	22%	14%
11–20	26%	28%	39%
21–30	25%	26%	25%
>30	33%	25%	23%
Endocrinologists	94%	93%	97%
University practice	30%	37%	62%
Private Practice	33%	28%	26%
Most likely explanation for normal TSH on LT4 but persistent Symptoms (Agree or Strongly Agree)			
Psychosocial factors	78%	77%	82%
Chronic fatigue syndrome	48%	59%	80%
Comorbidities	73%	70%	78%
Burden of taking medication	35%	33%	53%
Chronic disease burden	58%	55%	46%
Inflammation/auto-immunity	39%	27%	49%
Inability of LT4 to restore normal physiology	20%	23%	46%
Control over thyroid hormone formulation prescribing	51%	78%	95%
Use of dietary supplements at the request of the patient	52%	29%	31%
Use of LT4/LT3 containing regimens	65%	15%	4%
Use of thyroid hormone for euthyroid patients with			
Depression	13%	6%	5%
Female infertility	46%	41%	39%
Goiter	17%	28%	10%
Hypercholesterolemia	8%	6%	6%
Obesity	6%	5%	6%
Fatigue	8%	7%	9%
Never Indicated	46%	43%	53%
Preferred formulations			
Poor control despite taking correctly-liquid/soft gel	44%	52%	34%
Intolerance or GI conditions-no difference	13%	17%	20%
Good control but persistent symptoms-liquid/soft gel	18%	9%	11%
Use of non-LT4 regimens for self management of hypothyroidism	34%	17%	11%

misattributed to hypothyroidism.³¹ Our survey results are consistent with these conclusions.

In accordance with current guidelines,^{2–4} 100% of AACE respondents indicated that LT4 is their first choice of therapy for hypothyroidism. However, a study of 2 large national U.S. patient claims databases on new prescriptions of thyroid hormone defined as written within 12 months of diagnosis of hypothyroidism showed that 87.2% received LT4 monotherapy, 2.7% LT3, and approximately 10.2% DTE.³² This difference in prescribing DTE as initial treatment for hypothyroidism between our respondents and national claims data contrasts with the responses by both endocrinologist and non-endocrinologist AACE members (0% versus 10.2%). Other reasons underscored by our survey for why DTE would not be prescribed as first line treatment include concerns about patients experiencing thyrotoxic symptoms on DTE, safety in patients with comorbidities and lack of good quality evidence in favor of DTE use (data not shown).

The principal drivers for switching from LT4 to combination therapy or DTE were persistent symptoms or not feeling well, low serum T3 level, which is not recommended as a diagnostic or monitoring tool in hypothyroidism,^{2,3} and patient requests. Persistent symptoms and patient pressure on physicians to prescribe combination therapy have been cited in previous U.S. surveys.^{24,25} The low serum T3 argument in favor of LT3-containing treatments is based on the observation that borderline low or subnormal serum T3 levels occur in a significant minority of patients treated with LT4; however, the evidence suggests that symptoms or quality of life do not correlate with serum T3 levels.^{33,34} Despite the evidence cited above, several high profile

reviews and commentaries by opinion leaders have expressed views in favor of use of LT3 in hypothyroidism, extrapolating from animal models, which have probably been influential in shaping respondent opinions.^{35–37}

Multivariate analysis in our study identified associations between some demographic factors (male gender, medical education in the U.S. and group practice settings), and a higher likelihood to prescribe LT4/LT3 or DTE, while age>70 and government/military practice were associated with a lower likelihood.

Aggregate data from 28 European THESIS surveys have shown similarities to our survey, but there are some notable differences.³⁸ U.S. respondents were much more likely to use LT4/LT3, DTE, and dietary supplements than Europeans. This may be related to the fact that DTE, though not FDA-approved, is more easily accessible in the U.S. than in European countries.

In order to further understand the decision process for use of LT3-containing regimens in hypothyroidism, we invited opinions about the underlying causes of persistent symptoms and whether respondents would consider such treatments for themselves. Respondents attributed persistent symptoms to psychosocial factors (78%), unrealistic patient expectations (75%), and comorbidities (74%). While 60% would consider treating their patients with persistent symptoms with LT3-containing therapies, only 34% would choose to be treated with combination LT4/LT3 or DTE themselves.

Our survey indicates that a substantial number of respondents, for reasons that were not explored, did not follow evidence-based guideline recommendations by the ATA and similarly, by the 2020 American, European, and British Thyroid Associations Consensus statement.^{3,28}

Thyroid Hormone Treatment in Patients with Euthyroidism

We examined the use of thyroid hormone in euthyroid individuals with female infertility and positive thyroid antibodies, obesity, depression, hyperlipidemia, fatigue, and goiter. It was highest for thyroid peroxidase antibody-positive, infertile women (nearly half of all respondents) and varied between 6% and 14% for others (goiter, depression, obesity, hypercholesterolemia, fatigue). The 2017 guidelines of the American Thyroid Association, which state that there is insufficient evidence for or against LT4 treatment in this scenario, may have influenced the use of thyroid hormone in the setting of female infertility and positive antibodies,³⁹ despite subsequent randomized controlled studies demonstrating no benefit of LT4 treatment on pregnancy outcomes.^{15–17}

Limitations

The main limitation of our study was the low response rate. While the survey invitation was sent to 4000 U.S. AACE members, only 7% completed it. Use of the survey link clicks to calculate the response rate (77%) was calculated as another gauge of engagement.⁴⁰ The survey was only sent to U.S. AACE members; however, 2% did not confirm that they were members, perhaps because of membership lapse or other explanations. As the link did not require a unique log in, nor were respondents identified, it is also possible the survey was forwarded to non-members or was completed more than once by the same individual. Survey questions did not specify whether the respondent was the first clinician to treat the patient for hypothyroidism, which may have affected answers to choice of treatment. It is also unclear to what extent treatment decisions were patient-driven versus clinician-driven. Survey respondents were not asked whether they based management decisions on published guidelines versus more recent studies; for example in the case of the 2019 trial examining management of euthyroid, antibody positive pregnant women, which was published after the 2017 ATA guidelines.^{15,39} Despite these limitations, respondent characteristics were similar to nationally published figures and those of other physician surveys on hypothyroidism conducted in the U.S., and the absolute numbers of participants were comparable to other surveys. Thus, we believe the study provides valuable insights into current practice on the treatment of hypothyroidism by endocrinologists and endocrine care team members in the U.S.

Conclusions

In accordance with several other studies, LT3-containing thyroid regimens are used by U.S. endocrinologists and endocrine care team members for patients who are dissatisfied with LT4 treatment, and LT4 is used in a significant proportion of patients with euthyroidism. A novel finding was that contrary to national U.S. prescription data for overall use of DTE in about 10% of newly diagnosed patients with hypothyroidism, U.S. AACE members in our survey were unanimously against commencing therapy of hypothyroidism with LT4/LT3 combination therapy. Patient preference, clinician experience, practice setting, geographic and healthcare system factors were associated with variation in evidence-based practice. Better approaches to implementing regularly updated, evidence-based guidelines for treating hypothyroidism are required.

Disclosure

The authors have no conflicts of interest to disclose.

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