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Assesment of attainment of recommended TSH levels and levothyroxine compliance in differentiated thyroid cancer patients

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Abstract

Objective: Thyroid-stimulating hormone (TSH) suppression treatment can induce signs and symptoms of hyperthyroidism and hypothyroidism due to inappropriate treatment or poor compliance to the treatment. The current study aimed to

investigate TSH levels, frequency of being on target TSH, adherence to levothyroxine (LT4) suppression treatment in differentiated thyroid cancer (DTC) patients after surgery in a multicentric setting.

Design and Patients: This multicentric cross-sectional study was conducted at 21 medical centres from 12 cities in Turkey. DTC patients followed at least one year in the same center included in the study. Clinical data, serum TSH, free thyroxine (FT4), thyroglobulin (Tg) and anti-Tg levels were recorded during the most recent visit. Body mass index, systolic and diastolic blood pressures, pulse rate were measured. LT4 doses were recorded and doses per kilogram of bodyweight were calculated. Pill ingestion habits recorded and adherence to the therapy were evaluated using the Morisky Medication Adherence Scale and categorized as good, moderate or poor compliant based on their scores. Risk stratification forpredicting the disease persistance and/or reccurence was assessed using the American Joint Committee on Cancer-7th edition thyroid cancer staging calculator. TSH serum concentrations were classified as severe suppression (TSH < 0.01 mU/L), moderate suppression (TSH: 0.01–0.1 mU/L), mild suppression (TSHL 0.1–0.5 mU/L), euthyroid (TSH: 0.5–4 mU/L) and hypothyroid (TSH > 4 mU/L). TSH levels can also be classified as on being on target, under the target, or beyond over the target, according to the American Thyroid Association recommendations.

Results: A group of 1125 patients (F/M: 941/184, 50.7 ± 11.7 years) were included in the study. The mean LT4 daily dosage was 132.4 ± 39.6 mcg/day. TSH levels showed severe suppression in 99 (%8.8) patients, moderate suppression in 277 (% 24.6) patients and mild suppression in 315 (%28) patients and euthyroid range in 332 (%29.5) patients and hypothyroid range in 97 (8.6%). TSH levels were in target in 29.2% of the patients 20.4% of the patients were undertreated, 50.4% overtreated. The daily LT4 dose and LT4 dose/kg were significantly higher in the severe suppression group ($p < .001$, $p < .001$). According to the Morisky scale, 564 patients (50.1%) were good compliant, 368 patients (32.7%) were moderate compliant, and 193 patients (17.1%) were noncompliant. Patients with poor compliance need a higher dose of LT4 compared to the good compliance group ($p < .001$). TSH levels of patients with good compliance were 0.67 ± 1.96 mU/L and TSH with poor compliance was 2.74 ± 7.47 mU/L ($p < .001$). TSH levels were similar in patients on fixed and alternating dosages.

Conclusion: In 29.2% of the DTC patients, serum TSH levels were at target levels. Remaining of the study group have TSH levels under or over treatment range, exposing the patient to medication side effects. Majorty of the study group 82.8% have good or moderate adherence to LT4 therapy. Reaching TSH targets requires simplified and applicable guidelines and following the guideline recommendations.

KEYWORDS

hormones/related, levothyroxine, thyroid, thyroid cancer, thyroid function tests, thyrotropin

1 | INTRODUCTION

Thyroid-stimulating hormone (TSH) suppression treatment is a standard follow-up treatment for patients with differentiated thyroid carcinoma (DTC) following surgery to reduce the rate of recurrence and cancer-related mortality, particularly in high-risk patients.[1] The rationale for utilizing this medication is that TSH receptors are located in both thyrocytes and thyroid cancer cells, and lower TSH levels impede cancer cell proliferation.[2] After surgery, levothyroxine (LT4) is used to prevent hypothyroidism, and supraphysiologic LT4 doses are recommended to suppress TSH levels depending on the patient's risk status.[1]

Retrospective and prospective studies have demonstrated that TSH suppression to below 0.1 mU/L may prevent recurrence in high-risk thyroid cancer patients.[3–6] However, no such evidence of benefit has been documented in low-risk patients.[4,7–9] A meta-analysis supported the efficacy of TSH suppression therapy in preventing major adverse clinical events such as disease progression, recurrence, and death.[6]

In a study conducted in the population with advanced differentiated thyroid cancer, the prognosis was impaired in patients with TSH > 1 mU/L. Still, no further improvement in prognosis was detected in patients with TSH < 0.03 mU/L compared with patients with TSH 0.1–0.03 mU/L.[10] According to long-term follow-up results of a multi-institutional registry study, moderate TSH suppression treatment was associated with better outcomes, and aggressive TSH suppression did not have an additive effect on prognosis even in patients with distant metastasis.[11] TSH suppression was also not associated with overall survival or disease-free survival in intermediate and high-risk patients, according to the findings of a recent cohort study.[12] Individual TSH goals must establish a balance between the potential benefit of TSH suppression and the risk of subclinical thyrotoxicosis. Aggressive TSH suppression can induce cardiovascular disease and osteoporosis.[13,14] LT4 medication has a limited therapeutic index, which emphasizes the importance of drug adherence in achieving ideal TSH levels. Drug adherence is a dynamic process that is closely linked to treatment outcomes in patients with chronic diseases, and it is vital for thyroid cancer patients to achieve and maintain therapeutic TSH levels.

There is limited information on the number of thyroid cancer patients who achieve TSH targets under LT4 suppression treatment. Grani et al.[3] investigated the effect of LT4 doses in athyreotic individuals secondary to DTC and discovered that TSH variations are common in patients on stable doses. In this current study, we investigated TSH levels and the status of reaching target TSH according to risk status and adherence to LT4 treatment and related factors of treatment adherence in DTC patients after surgery in a multicentric setting.

2 | MATERIALS AND METHODS

This is a cross-sectional outpatient study conducted at 21 medical centres in 12 cities (Istanbul, Kocaeli, Manisa, Bursa, Eskisehir, Malatya, Diyarbakir, Adana, Usak, Batman, Bolu, Tekirdag) in different regions of Turkey. The study was approved by the Local Ethics Committee of Marmara University School of Medicine, Istanbul (09.2017.359) and conducted in compliance with the Declaration of Helsinki.

2.1 | Patients selection

This cross-sectional multicentric study included a group of 1125 patients with DTC after total and subtotal thyroidectomy and followed-up under LT4 suppression treatment for at least 1 year. Patients with central hypothyroidism, inflammatory bowel disease, malabsorption syndrome, gastric bypass surgery, other malignancy or medullary or anaplastic thyroid cancer, and those receiving tri-iodothyronine (T3) therapy, pregnant women and lactating women and patients diagnosed as DTC in less than 1 year were excluded from the study.

2.2 | Clinical evaluation

From medical records, clinical data such as age, sex, disease duration, surgical type (total or lobectomy), radioactive iodine treatment and dosage and comorbid diseases (diabetes mellitus, hypertension, cerebrovascular disease, coronary artery disease, atrial fibrillation, malabsorption, inflammatory bowel disease, gluten enteropathy) were obtained. Data from pathology reports was transcribed from files. The daily LT4 doses and treatment plans were recorded. The amount of LT4 per kilogram was computed. Bodyweight and height are assessed, and body mass index (BMI) is determined as kg/m^2 using the BMI formula. After 15 min of rest, the systolic and diastolic blood pressures (DBPs), as well as the pulse rate (PR) per minute, were assessed.

2.3 | Risk evaluation at the time of diagnosis

At the time of diagnosis, the stage and risk of metastasis/recurrence were assessed using American Thyroid Association (ATA) guidelines. In the previous visit, the American Joint Committee on Cancer 7th edition re-evaluated thyroid cancer risk using the thyroid cancer staging calculator, based on the ATA 2015 guidelines.[1] Staging criteria include age at diagnosis, gender, tumour size, invasion, surgery type, lymph node metastasis, distant metastases, multifocality and anaplastic type.

2.4 | Laboratory evaluation

At the last visit, serum TSH, free thyroxine (FT4), serum thyroglobulin (Tg), and anti-Tg were recorded from the patient files. Thyroid hormones were measured at the laboratories of the hospitals where the patients were followed with the third-generation chemiluminescence immunoassay method. Reference ranges of TSH and FT4 were similar between laboratories. The reference range for TSH was

0.34–5.60 mU/L, and for FT4 was 0.61–1.12 ng/dl (0.144–0.26 pmol/L). The minimum detectable TSH level was 0.01. Before taking the pill, venous blood samples for thyroid function analysis were collected after an 8-h fasting in the morning.

Target TSH levels are accepted according to ATA 2015 guidelines. The guideline recommends target TSH levels to be kept <0.1 mU/L in high-risk patients and 0.1–0.5 mU/L in intermediate-risk patients. After evaluation for remission, if there is not a structural disease, titration of TSH levels between 0.1 and 0.5 mU/L at least 5 years is recommended in high-risk patients. There is no evidence of suppression treatment in intermediate and low-risk patients if there is no structural disease, keeping TSH levels between 0.5 and 2 mU/L.[1] Patients were classified according to TSH levels as severe suppression (TSH < 0.01 mU/L), moderate suppression (TSH: 0.01–0.1 mU/L), mild suppression (TSH: 0.1–0.5 mU/L), normal (TSH: 0.5–4 mU/L) and hypothyroid (TSH > 4 mU/L).

Patients were also classified according to reaching TSH target levels adjusted to duration of disease, risk and remission status, as at target or not.

2.5 | Adherence to LT4 therapy

Through an interview, we were able to learn about the patients' LT4 administration practices. The questions revolved around pill ingestion time, mealtime after taking the pill, concomitant pill ingestion (proton pump inhibitors, multivitamins, iron, antihypertensive pills, oral antidiabetics, anticonvulsants, etc.), taking the pill with water or other liquids (juice, soda, milk, tea, coffee), and taking daily alternate or fixed LT4 dosage.

All participants were administered the eight-item Morisky Medication Adherence Scale (MMAS-8), a structured self-reporting medication adherence test. MMAS-8 consists of seven yes/no questions and one 5-point Likert scale which evaluates the drug-taking behaviour as forgetfulness, feeling hassled about sticking to the treatment plan, stopping the regimen because the medication makes the patient feel worse or not taking the drugs when leaving home/travelling. Patients who scored eight points were classified as good compliant, those who scored 6–8 points were classified as moderate compliant, and those who scored less than six points were classified as poor compliant.

2.6 | Statistical analysis

The distribution of the data was analysed by Shapiro–Wilk test. One way analysis of variance (ANOVA) test was used for comparing the data showing normal distribution among three groups. The Kruskal–Wallis ANOVA test was used to compare variables that did not have a normal distribution among three groups. The Fisher exact test was used to examine the differences between categorical data sets. Post-hoc comparisons of the variables that were found meaningful after the ANOVA and Kruskal–Wallis tests were analysed by the Dunn test. Descriptive statistics of data for numerical variables: average, standard deviation, median, minimum and categorical variables were given frequency. All analyses were conducted by the IBM Statistics 22.0 Programme within the 0.05 significance level.

TABLE 1 Clinical and laboratory characteristics of the DTC patients

	Total (n = 1125)	Women (n = 941)	Men (n = 184)	p-value
Age (years)	50.7 ± 11.7	50.4 ± 11.5	52.2 ± 12.3	.32
Duration of disease (years)	5.08 ± 4.39	5.15 ± 4.37	4.72 ± 4.52	.11
BMI (kg/m^2)	30.39 ± 5.84	30.67 ± 6.04	28.9 ± 4.41	<.001
SBP (mmHg)	125.1 ± 19.4	124.7 ± 19.2	127.3 ± 20.7	.033
DBP (mm/Hg)	77.8 ± 11.83	77.5 ± 11.7	79.5 ± 12.2	.064
Pulse (per minute)	79.92 ± 10.5	79.5 ± 10.3	82.05 ± 11.6	.036
LT4 daily dosage (mcg/day)	132.4 ± 39.6	128.5 ± 38	152 ± 42	<.001
LT4 dose (mcg/kg)	1.71 ± 0.53	1.69 ± 0.54	1.79 ± 0.45	.002
TSH (mU/L)	2.26 ± 10.2	2.28 ± 10.46	2.16 ± 9	.55
FT4 (ng/dl)	3.14 ± 4.65	2.26 ± 10.43	3.12 ± 4.6	.38
TSH				.96
<0.1	378 (30.9%)	312 (33.1%)	66 (35.8%)	
0.1–0.5	314 (27.9%)	265 (28.1%)	49 (26.6%)	
0.5–4	330 (29.3%)	283 (30.1%)	47 (25.5%)	
>4	103 (9.1%)	81 (8.6%)	22 (11.9%)	

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; DTC, differentiated thyroid cancer; FT4, free thyroxine; LT4, levothyroxine; SBP, systolic blood pressure; TSH, thyroid-stimulating hormone.

TABLE 2 Clinical and laboratory parameters of the patients with mild, moderate and severe TSH suppression

	Severe suppression (*N* = 99)	Moderate suppression (*N* = 277)	Mild suppression (*N* = 315)	Nonsuppressed (*n* = 434)	*p*-value
Age (years)	49.4 ± 11.4	49.5 ± 10.7	50.97 ± 11.96	51.5 ± 12.12	.9
Duration of disease (years)	3.8 ± 3.5*	4.2 ± 3.8*	5.5 ± 4.2	5.6 ± 4.9	<.001
Risk score (*n*) (high/low)	29/79 (29.2%/60.8%)	79/198 (28.5%71.5%)	71/244 (22.5%/77.5%)	86/348 (19.8%/80.2%)	.69
BMI (kg/m^2)	28.5 ± 5.09$^+$	29.7 ± 6.32	30.6 ± 6.03	31 ± 5.8	.02
SBP (mmHg)	117.9 ± 14.7$^+$	125.8 ± 19.3	123.09 ± 18.5	128 ± 21	<.001
DBP (mmHg)	75.1 ± 11.1$^{\&}$	78.7 ± 11.9	75.6 ± 11.3$^{\&\&}$	79 ± 12	.0025
Pulse (per minute)	80.3 ± 9.3	81 ± 9.8	79.6 ± 10.7	79 ± 11	.23
Daily LT4 dose (mcg/day)	138.1 ± 40.3*	138.7 ± 40.3*	131.9 ± 38.9	127 ± 39	<.001
LT4 dose (mcg/kg)	1.89 ± 0.53**	1.8 ± 0.49***	1.69 ± 0.6$^+$	1.6 ± 0.48	<.001
TSH (mU/L)	0.009 ± 0.002	0.042 ± 0.024	0.25 ± 0.11	5.6 ± 16	<.001$^{\#}$
FT4 (ng/dl)	3 ± 4.8	3.4 ± 5	3 ± 4.5	3.2 ± 4.5	<.001$^+$
Morinsky score					.4
Good	58 (58.5%)	152 (54.8%)	164 (52%)	190 (43.7%)	
Moderate	32 (32.3%)	87 (31.4%)	99 (31.4%)	151 (34.7%)	
Low	9 (9%)	31 (11.1%)	42 (13.3%)	80 (18.4%)	

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; DTC, differentiated thyroid cancer; FT4, free thyroxine; LT4, levothyroxine; SBP, systolic blood pressure; TSH, thyroid-stimulating hormone.

$^+$Severe suppression versus mild, moderate and nonsuppressed.

$^{\&}$Severe suppression versus moderate and nonsuppressed.

$^{\&\&}$Mild suppression versus moderate and nonsuppressed.

$^{\#}p < .05$ for nonsuppressed versus mild, nonsuppressed versus moderate, nonsuppressed versus severe, mild versus moderate, mild versus severe, moderate versus severe.

*$p < .001$ versus nonsuppressed group.; **$p < .001$ versus mild, moderate and nonsuppressed groups.; ***$p < .001$ versus mild and nonsuppressed.

$^+p < .001$ versus nonsuppressed.

$^{++}$Significant for nonsuppressed versus mild, nonsuppressed versus moderate, nonsuppressed versus severe, mild versus moderate.

3 | RESULTS

3.1 | Clinical characteristics of the patients

A total of 1125 DTC patients (F/M: 941/184) were enroled in this multicentric study. The mean age was 50.7 ± 11.7 years and the mean duration of disease was 5.08 (4.39 years). The study group's clinical and laboratory characteristics according to gender are shown in Table 1. BMI was higher in women than men ($p < .001$), systolic blood pressure (SBP) ($p = .037$), PR ($p = .036$) were higher in men compared to women. The mean LT4 daily dosage was 132.4 ± 39.6 mcg/day. LT4 dosage was higher in men than women group ($p < .001$). The mean TSH of the patients was 2.26 ± 10.2 mU/L. A total of 33.4% of the patients had TSH < 0.1 mU/L, and 8.6% of the patients were hypothyroid.

3.2 | Analysis of the patients according to TSH suppression level

The clinical and laboratory findings of the patients according to TSH suppression level are shown in Table 2. The group with severe suppression had a BMI that was significantly lower ($p = .02$) than the control group. LT4 dose and LT4 dose/kg of the nonsuppressed group were significantly lower ($p < .001$, $p < .001$). The SBP ($p < .001$) and DBP ($p = .0025$) of the nonsuppressed group were significantly higher.

The patients were categorized according to risk and remission status, with adjusted TSH target levels. A total of 50.4% ($n = 568$, 113 high-risk, 455 low-risk) of the patients were under overtreatment, and 80.2% were low-risk patients. 20.4% ($n = 228$, 115 high risk, 214 low risk) of the patients were undertreated and only 29.2% ($n = 329$) were on TSH target (Table 3).

TABLE 3 Characteristics and laboratory findings of patients according to being on target TSH levels or not

	At target ($N = 329$)	Overtreated ($n = 568$)	Undertreated ($N = 228$)	p-value
Age (years)	51.02 ± 12.2	50.4 ± 11.2	51.07 ± 12.4	<.001[a]
Duration of disease (years)	5.43 ± 4.96	5.16 ± 3.99	4.39 ± 4.43	<.001[b]
BMI (kg/m^2)	30.7 ± 6.1	30.08 ± 5.6	30.6 ± 5.8	.32
SBP (mmHg)	124.1 ± 20	123.8 ± 18.6	129 ± 20	<.001[b]
DBP (mmHg)	77.3 ± 11.8	77.2 ± 11.6	80 ± 11.98	.042
Pulse (per minute)	79.9 ± 9.89	80.5 ± 10.2	78.3 ± 12.1	.03[c]
LT4 daily dosage (mcg/day)	131.6 ± 38	134.3 ± 38.9	128.6 ± 43.2	.07
LT4 dose (mcg/kg)	1.7 ± 0.6	1.75 ± 0.48	1.64 ± 0.53	.06
TSH (mU/L)	0.62 ± 0.74	0.12 ± 0.13	9.84 ± 21.08	<.001[d]
FT4 (ng/dl)	2.74 ± 4.25	3.21 ± 4.81	3.51 ± 4.77	.01[e]

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; FT4, free thyroxine; LT4, levothyroxine; SBP, systolic blood pressure; TSH, thyroid-stimulating hormone.

[a]Overtreated versus at target and at target versus undertreated.

[b]Overtreated versus undertreated and at target versus undertreated.

[c]Undertreated versus overtreated.

[d]Overtreated versus at target, overtreated versus undertreated, at target versus undertreated.

[e]At target versus undertreated.

TABLE 4 Clinical characteristics of patients according to drug adherence status

	Good compliance ($N = 564$)	Moderate compliance ($N = 368$)	Poor compliance ($N = 193$)	p-value
Age (years)	52.4 ± 11.3[a]	49.8 ± 11.3	47.2 ± 12.4	<.001
BMI (kg/m^2)	30.26 ± 5.3	30.3 ± 5.6	30.23 ± 7.5	.549
Duration of disease (years)	5.2 ± 4.6	4.8 ± 3.8	5.1 ± 4.6	.89
LT4 daily dosage (mcg/day)	128.3 ± 34.8	133.02 ± 41.38	143.5 ± 47.16	<.001[b]
LT4 dose (mcg/kg)	1.63 ± 0.46	1.72 ± 0.51	1.76 ± 0.84	.0013[c]
Fix/alternate dose (n/%)	325/239 (57.6%/42.4%)	197/171 (58.5%/42.5%)	130/63 (67.3%/32.7%)	.32
TSH (mU/L)	0.67 ± 1.96	1.29 ± 3.08	2.74 ± 7.47	<.001[d]
FT4 (ng/dl)	2.95 ± 3.78	2.65 ± 3.62	1.91 ± 3.04	.171

Abbreviations: BMI, body mass index; FT4, free thyroxine; LT4, levothyroxine; TSH, thyroid-stimulating hormone.

[a]Significant for the good compliant versus moderate compliant and poor compliant.

[b]Significant for good versus moderate, moderate versus poor.

[c]Good versus poor.

[d]Good versus poor, moderate versus poor.

3.3 | Analysis of patients according to LT4 ingestion patterns and drug adherence

According to drug ingestion pattern data, 7.6% ($n = 85$) of patients missed their dose at least once in the last week, and 16.4% ($n = 185$) of the patients missed their dose at least once for the last month. A total of 99% of the patients were taking the drug before breakfast. Two hundred forty-nine patients (22.1%) were taking the drug less than 30 min before the breakfast, 539 patients (47.9%) were taking 30–60 min before breakfast, and 326 patients (29%) were taking more than 60 min before the breakfast. Nine hundred eighty-two patients (87.3%) were taking the drug alone. One hundred thirty-four patients were taking their drug with another drug, and 60 of them were taking it at the same time with proton pump inhibitors.

All patients were subjected to the Morinsky drug adherence scale, 50.1% were good compliant, 32.7% were moderate compliant and 17.1% were poor compliant. Clinical and laboratory characteristics of patients according to compliance status were shown in Table 4. Good compliant

TABLE 5 Analysis of subjects according to drug intake

	Alternate dose (*N* = 492)	Fix dose *n* (*N* = 633)	*p*-value
Age (years)	51.44 ± 11.04	50.16 ± 12.21	.609
Duration of disease (years)	5.37 ± 4.43	4.85 ± 4.35	.01
BMI (kg/m^2)	30.40 ± 5.72	30.38 ± 5.94	.93
SBP (mmHg)	127.6 ± 19.6	123.2 ± 19.12	.012
DBP (mmHg)	79.11 ± 11.81	76.89 ± 11.76	.007
Pulse (per minute)	78.89 ± 10.75	80.70 ± 10.35	.012
LT4 daily dosage (mcg/day)	127.4 ± 33.97	136.2 ± 43.19	.002
LT4 dose (mcg/kg)	1.65 ± 0.42	1.76 ± 0.59	.01
Morinsky score			.732
Good	239 (48.5%)	325 (51.3%)	
Moderate	171 (34.7%)	197 (31.1%)	
Low	63 (12.8%)	100 (15.7%)	
TSH (mU/L)	1.25±3.65	3±13.2	.47
FT4 (ng/dl)	2.91±4.46	3.32±4.8	<.001
TSH			.8
<0.1	166 (33.7%)	212 (33.4%)	
0.1–0.5	145 (29.4%)	170 (26.8%)	
0.5–4	146 (29.6%)	183 (28.9%)	
>4	35 (7.1%)	68 (10.7%)	

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; FT4, free thyroxine; LT4, levothyroxine; SBP, systolic blood pressure; TSH, thyroid-stimulating hormone.

patients were older ($p < .001$) compared to other groups The daily LT4 dose and LT4 dose/kg of the patients with poor compliance were significantly higher ($p < .001$, $p = .0013$). The mean TSH of the patients with poor compliance was 2.74 ± 7.47 mU/L and significantly higher than patients with good (TSH: 0.67 ± 1.96 mU/L) and moderate compliance (TSH: 1.29 ± 3.08 mU/L) ($p < .001$).

According to MMAS-8, undertreated patients were 38% good compliant, 37.2% were moderate compliant, and 24.8% were poor compliant. On target patients were 50.5% good compliant, 37% were moderate compliant, and 12.5% were poor compliant. Overtreated patients were 54.8% good compliant, 33.7% moderate compliant and 11.6% poor compliant. Patients were evaluated according to the LT4 dosing schedule as fixed-dose or alternate dose. Four hundred ninety-two patients were taking LT4 as an alternate dose. The daily LT4 dose and LT4 dose mcg/kg were higher in patients taking fixed doses ($p = .002$, $p = .01$). FT4 levels of patients taking fixed doses were significantly high ($p < .001$). TSH levels were similar between groups. The SBP ($p = .012$) and DBP ($p = .007$) of patients taking alternate doses were significantly high. The pulse per minute of patients taking fixed doses was significantly high ($p = .012$). The characteristics of patients according to dosing schedule are shown in Table 5.

4 | DISCUSSION

LT4 treatment is a routine treatment modality for postsurgical follow-up of patients with DTC. According to ATA 2015 guidelines, TSH suppression is recommended for high-risk patients for 5 years and intermediate-risk patients as initial management. TSH suppression is not recommended for low-risk patients and follow-up of intermediate-risk patients. However, to date, there has not been a large-scale study conducted in a large population about the drug adherence and TSH target reaching ratios of patients in actual clinical practice. In this current study, we evaluated the patients for their TSH levels, TSH suppression status and reaching target TSH levels according to risk status, drug ingestion patterns and drug adherence status. According to the results of this study, only 29.2% of the patients were on TSH target levels. A total of 50.4% of the patients were under overtreatment and faced overtreatment's potential side effects. In a recent study from China, 61.4% of the patients were found to have achieved TSH target levels.[15]

In this study group, 99% of the patients took their drug before breakfast, but 22.1% ate their breakfast in less than 30 min after taking the drug. A total of 17.1% of the patients were poor compliant to medication according to MMAS-8. According to the results of a recent study enroled in patients with thyroid cancer, 52% were found to be nonadherent to LT4; compared to this study, the population in this current study was good compliant with their medication.[16] Most of the studies about LT4 adherence in literature were enroled in patients with hypothyroidism and the ratio of the patients with good adherence was heterogenous in a range of 31.3%–87%.[17–21] A total of 82.9% of patients in this study were good and moderate compliant but most of the patients were far from TSH target levels; half of the patients were using higher doses of LT4 from their need. This could be due to the aggressive approach of doctors in suppressing TSH levels or their failure to do a risk assessment at follow-up. This issue could also be caused by the complexity of current guidelines in overcrowded outpatient clinics. Half of the patients in this cohort are at risk of developing subclinical or overt hyperthyroidism, which can cause osteoporosis, cardiac problems and cognitive side effects.[8]

In this study, the poor compliance ratio of patients who were undertreated was higher, as were the FT4 levels of these patients. This could be associated with irregular drug use or utilizing the substance on a regular basis before the outpatient clinic visit. The LT4 doses were also higher among patients with poor compliance, which could be associated to irregular drug use. The TSH levels of the patients taking the drug as fixed-dose or alternate dose were similar, but the FT4 levels of the patients taking fixed-dose were higher. This may be due to relatively high doses of the patients taking fixed doses in the last few days before taking blood samples.

In the literature, there is no study about the TSH status of DTC patients in clinical practice, and we do not know how well the guideline could be followed. The strength of this study is the multicentric design of

the research; this study was enroled in a large patient population from different endocrinology and metabolism clinics in other cities. As a limitation, this is a cross-sectional study, and only one TSH level was evaluated for each patient. The laboratory analysis of the patients was done in different centres participating in the study. Also, there is a validation for the Turkish version of MMAS-8, but the Turkish version of MMAS-8 was not validated for patients using LT4, which is also a limitation of this study.

In conclusion, this study indicates that in clinical practice, the target TSH reaching frequency of the DTC patients are low. Most of the patients are under over and under treatment. Patients are exposed to the side effects of hyperthyroidism and hypothyroidism. To prevent side effects from overtreatment, risk assessment during follow-up and revising the target TSH value are essential. More straightforward and clinically applicable guidelines may help prevent this situation.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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