

Self-reported medication adherence in differentiated thyroid cancer survivors: Role of illness perception and medication beliefs

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Abstract

Background: To investigate medication adherence (MA) to Levothyroxine in differentiated thyroid cancer survivors and analyze the related factors for nonadherence.

Methods: The Medication Adherence Report Scale (MARS), Hospital Anxiety and Depression Scale (HAD), Brief Illness Perception Questionnaire (B-IPQ), and Beliefs about Medicines Questionnaire (BMQ) were used to assess MA.

Results: Nonadherence was reported in 77 of 197 patients (39.1%). Socioeconomic status and education levels were found to be significantly related to MA. The HAD scores, all items of B-IPQ, and BMQ were associated with MA and showed a correlation with the MARS scores. The primary predictors of MA were greater confidence in treatment modality (odds ratio [OR]: 0.48, 95% confidence interval (CI): 0.37-0.63) and greater belief that the medication had minimal risk of harm (OR: 3.35, 95% CI: 1.50-7.49).

Conclusions: Special attention should be paid to educational programs for differentiated thyroid carcinoma patients concerning the effectiveness and low risk of harm of medication in order to improve MA.

KEYWORDS

differentiated thyroid cancer, levothyroxine, medication adherence, medication beliefs

1 | INTRODUCTION

Thyroid cancer is the most common endocrine malignancy accounting for around 1% of all new malignant diseases diagnosed each year.¹ Approximately 94% of these are differentiated thyroid carcinomas (DTCs) derived from thyroid epithelial cells including papillary and follicular thyroid histology. The initial management for most patients with DTC is usually surgery, in the form of hemithyroidectomy or total thyroidectomy.^{1,2} Surgical resection is often followed by adjuvant radioiodine therapy, and life-long thyroid hormone replacement therapy.

Thyroid-stimulating hormone (TSH) suppression is recommended to rectify postsurgical hypothyroidism. In addition, thyroid hormone administered in doses suppressing TSH has been proposed as a therapeutic intervention in thyroid cancer since it provides both the slow growth and spread of thyroid cancer cells, and prevents disease recurrence in patients with DTC.³ In light of this information, thyroid hormone treatment plays a central role in the postoperative management of DTC. Levothyroxine (LT4) is a reliable and commonly prescribed drug to achieve targeted TSH levels. LT4 treatment keeps the TSH concentration in a narrow range,

which is considered as an important predictor for progression-free or disease-free survival.

Adherence is defined by the World Health Organization (WHO) as the degree to which the patients' accepts and follows the treatment organized by health care professionals. Personal behaviors including starting and completing a treatment program, attending follow-up sessions on time, using the prescribed medication at the recommended dose and time, following the recommended diet, and modifying life-style are fundamental determinants of medication adherence.^{1,4} Typically, adherence rates reaching 80% or higher are needed for optimal therapeutic efficacy in chronic diseases. Medication non-adherence is a particularly important challenge which prevents the achievement of expected outcomes in patients with long-standing, chronic diseases. Adherence is influenced by many factors, including patient-related psychological factors, therapy-related factors that encompass the unfavorable side-effects of medication, condition-related factors; for example, duration of therapy, and health care system, and socioeconomic factors referring to medication cost, health insurance, and family or social support.⁵ Additionally, "health literacy" defined as the degree to which an individual has the capacity to obtain, process, and understand basic health information to comply with treatment and make appropriate health decisions about his/her health, and thus is considered as a key point contributing to adherence.⁶

Drug adherence is a dynamic process which is closely linked with treatment outcomes in patients with chronic diseases. For a wide range of medical conditions, at least one effective drug therapy model is available, yet. Non-adherence remains a key challenge. It is estimated that only about 50% of patients follow treatment recommendations.⁷ Unfortunately, there is no gold standard method for monitoring patient compliance with drug regimes. Direct patient reports, clinical impression, measurements of drug concentrations or metabolites in blood, frequency of refills at the pharmacy, or electronic medication monitors can be used to investigate adherence to therapy, none of which seems to be feasible on an everyday basis.⁸

Further studies are required to improve medication adherence in terms of reducing treatment and care costs and improving quality of life. A review of the literature investigating medication adherence, shows that there are many studies on self-reported medication adherence in patients with long-standing, chronic diseases, such as diabetes mellitus, gout, hypercholesterolemia, hypertension, osteoporosis, seizure disorders, and ankylosing spondylitis.^{7,8} Hypothyroidism, a chronic condition with a simple treatment, has been demonstrated to be associated with high rates of nonadherence with an estimated range of

22% to 82%.⁹⁻¹² Despite various studies on hypothyroidism, to the best of our knowledge, no researcher has assessed all the aspects of medication adherence in patients with thyroid cancer who have undergone total thyroidectomy. Therefore, in this study, we aimed to investigate adherence to LT4 after DTC surgery and analyze the related factors for medication nonadherence.

2 | PATIENTS AND METHODS

2.1 | Study design

This cross-sectional study was conducted with 197 patients, aged 24 to 67 years (80 males and 117 females) who had undergone bilateral total thyroidectomy with or without central lymph node dissection performed by the same endocrine surgery team at Medipol University Faculty of Medicine, General Surgery Department between August 2012 and February 2019 and had final pathological reports showing (DTC) (papillary or follicular). All patients had been well informed about the disease characteristics, risk of recurrence, importance of TSH suppression, and the outcomes of adherence or nonadherence to lifetime LT4 treatment both verbally and through a booklet (Data S1). Patients who had been on LT4 substitution treatment in the tablet form for at least 12 months were included in the analysis of adherence. The exclusion criteria were as follows: (a) age <18 years, (b) inability to read and understand the booklet and questionnaires, (c) any psychiatric disorder, receiving any psychiatric treatments, or cognitive impairment, including dementia, (d) not attending follow-up (defined as not visiting a general surgeon or endocrinologist within the last 12 months), and (e) requiring assistance of a caregiver for any significant comorbidity, including stroke and metastatic cancer other than DTC. All participants were informed about the purpose of the study and signed the written informed consent form. The study was approved by the Ethics Committee of Medipol University (10840098-604.01.01-E.41155 decision number: 609) and conducted in accordance with the principles of the Declaration of Helsinki.

2.2 | Data collection and questionnaires

Patient-related and disease-related data were collected using a well-designed self-reported questionnaire in Turkish language composed of two different sections. Demographic characteristics, including age, gender, marital status, education level, smoking status, and monthly income constituted the patient-related part of the

questionnaire whereas disease-related questions concerned cancer type, time since surgery (months), type of surgery, surgical complications encountered, familial DTC history, follow-up interval, medical comorbidities, and regular drug use other than LT4.

Medication adherence was assessed using the Medication Adherence Report Scale (MARS)¹³; which is a five-item, structured self-reported questionnaire, to identify a variety of nonadherent behaviors, including tendency to avoid, forget or stop taking medication and tendency to adjust or alter the dose prescribed by the clinician. In contrast to other medication adherence scales with dichotomous responses, the number of items and range of response options in MARS, accentuate the dynamic pattern of the adherence phenomenon. The items of the scale are to be responded on a five-point Likert-scale from (1) “(always)” to (5) “(never)”. The cumulative score of MARS ranges from five to 25, with higher scores indicating higher levels of self-reported adherence to the corresponding medication. Since there is no definitive cut-off point to differentiate high from low adherence, in this study, scores of 20 or higher were considered to indicate high medication adherence, based on the positive skewing of the sample distribution, after consulting the developer of MARS by e-mail.¹⁴ This cut-off value was also the mean value in our study, representing 40% of total adherence score. Since the total MARS score is critical for the comparison with the rest of the study population and determination of the cut-off point of the scale, participants who did not respond to all items in MARS were excluded from the study. The current study used the Turkish version of MARS, which was previously validated for the measurement of treatment adherence in all chronic diseases which require long-term medication, with an internal consistency (Cronbach α) coefficient (.78) and total item correlations (ranging from .35 to .71), similar to those of the original version.¹⁵

The Brief Illness Perception Questionnaire (B-IPQ) has eight items using a 0 to 10 scale, and an additional casual question intended to capture the key components of the Illness Representations Model by examining patients' cognitive and emotional representations about their disease.¹⁶ The first five items are aimed to assess cognitive illness perceptions, namely, consequences (how much does your illness affect your life?), timeline (how long do you think your illness will continue?), personal control (how much control do you feel you have over your illness?), treatment control (how much do you think your treatment can help your illness?), and identity (how much do you experience symptoms from your illness?). Item 6 (how concerned are you about your illness?) and item 8 (how much does your illness affect you emotionally?) form the emotional illness representations, concern and emotions, respectively. Item

7 (How well do you feel you understand your illness?) assesses illness comprehensibility, that is, coherence. Finally, the assessment of causal representation is through an open-ended item which encourages patients to list the three most important causal factors about their illness (item 9).¹⁶ The maximum score in B-IPQ is 80, and higher scores indicate more negative perceptions.¹⁷

For the assessment of the anxiety and depression levels of the patients, the Hospital Anxiety and Depression Scale, consisting of seven questions concerning anxiety and seven questions related to depression, was used. Scoring anxiety and depression separately is crucial, although the anxiety and depression questions are interspersed within the questionnaire.¹⁸

The Turkish version of the Beliefs about Medicines Questionnaire (BMQ) was used to assess the treatment beliefs of the patients that had undergone surgery for thyroid cancer. BMQ contains 18 questions presented in two parts: general and specific beliefs about the concerned drug. The specific part investigates patients' beliefs about the medications prescribed for a specific condition (in this study LT4 treatment after DTC surgery). This part consists of two subscales related to personal beliefs about the need for medication to keep thyroid function test results in a normal range (specific-necessity) and concerns about the adverse effects (specific-concerns) of the medicine. The items in the general part of BMQ investigate total patient beliefs toward drugs. This part is divided into two subscales consisting of the total belief scale exploring patients' beliefs regarding the way doctors prescribe drugs (general-overuse) and the damage scale analyzing patient beliefs about the harmfulness of drugs (general-harm). Each question is scored based on a five-point Likert scale (1—strongly disagree, 2—disagree, 3—uncertain, 4—agree, 5—strongly agree). The scale of specific beliefs have five questions ranging from 5 to 25. Higher scores in the Specific-Necessity Subscale indicate stronger perceived benefits of use the prescribed drug to maintain health compared to personal needs. Higher scores in the Specific-Concerns Subscale indicate greater concern about the adverse effects of regular drug use. In the general beliefs scale, the harm and overuse subscales have five questions each, scored from 4 to 20, with higher scores in the former indicating a more negative point of view about drugs in general terms, and considering drugs as addictive and toxic substances, and higher scores in the latter representing more negative views of the way doctors prescribe drugs. The necessity-concerns differential (necessity beliefs) is calculated as the difference between the scores of the necessity and concern scales, and accepted as an indicator of an individual considering his/her personal need for a specific treatment based on his/her concerns about the harmfulness of the drug.¹⁹

TABLE 1 Sociodemographic and clinical characteristics of thyroid cancer survivors according to medication adherence

	Total (n = 197)	Low adherence [MARS median score < 20] (n = 77; 39.1%)	High adherence [MARS median score ≥ 20] (n = 120; 60.9%)	P
Age (years), median (min-max)	39 (22-67)	41 (24-67)	38 (22-67)	.132
Gender				.706
Male	80 (40.6)	30 (39)	50 (41.7)	
Female	117 (59.4)	47 (61)	70 (58.3)	
Marital status				.463
Single	57 (28.9)	20 (26)	37 (30.8)	
Married	140 (71.1)	57 (74)	83 (69.2)	
Education level				<.001
≤8 years	48 (24.4)	35 (45.5)	13 (10.8)	
>8 years	149 (75.6)	42 (54.5)	107 (89.2)	
Monthly income, TL				.001^a .003^b
2200-5000	46 (23.4)	28 (36.4)	18 (15)	
5000-10 000	110 (55.8)	39 (50.6)	71 (59.2)	
Higher than 10 000	41 (20.8)	10 (13)	31 (25.8)	
Years since surgery, median (min-max)	30 (6-80)	26 (6-80)	32 (6-80)	.597
Type of thyroid cancer				.280
Papillary	144 (73.1)	53 (68.8)	91 (75.8)	
Follicular	53 (26.9)	24 (31.2)	29 (24.2)	
Type of surgery				.620
Total thyroidectomy	157 (79.7)	60 (77.9)	97 (80.8)	
Total thyroidectomy + neck dissection	40 (20.3)	17 (22.1)	23 (19.2)	
Perioperative complication				n.a.
Non	162 (82.2)	62 (80.5)	100 (83.3)	
Hypoparathyroidism	13 (6.6)	5 (6.5)	8 (6.7)	
Temporary RLN paresis	21 (10.7)	9 (11.7)	12 (10)	
Permanent RLN paresis	1 (0.5)	1 (1.3)	-	
Family history of thyroid cancer, yes	30 (15.2)	9 (11.7)	21 (17.5)	.268
Frequency of medical examination				.945
0-3 months	48 (24.4)	20 (26)	28 (23.3)	
3-6 months	87 (44.2)	32 (41.6)	55 (45.8)	
6 months-1 year	45 (22.8)	18 (23.4)	27 (22.5)	
Longer than 1 year	17 (8.6)	7 (9.1)	10 (8.3)	
Comorbidity, yes	39 (19.8)	16 (20.8)	23 (19.2)	.782
Additional drug use, yes	40 (20.3)	14 (18.2)	26 (21.7)	.553
Smoking habit, yes	33 (16.8)	12 (15.6)	21 (17.5)	.725

Note: $P < .05$ accepted as significant and shown in bold.

Abbreviation: RLN, recurrent laryngeal nerve.

^a P : significant difference between 2200 and 5000 and higher than 10 000 TL groups.

^b P : significant difference between 2200 and 5000 and higher than 5000-10 000 groups.

2.3 | Statistical analyses

Data were analyzed using the Statistical Package for the Social Studies (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0, Armonk, New York). The Kolmogorov-Smirnov test was used to evaluate the normality of data. Frequency, percentage, median, minimum and maximum values were used for descriptive statistics. For the two group comparisons (adherent vs nonadherent), we used the chi-square test for categorical variables, and the Mann-Whitney *U* test for continuous data. Correlations were evaluated using Spearman's rank correlation analyses. A *P*-value of <.05 was considered statistically significant. A multivariate logistic regression analysis was performed to determine the risk factors for adherence. For a factor to be included in this regression model, the *P* value was accepted as .05 using the forward conditional method, and the *P*-value for exclusion was .1. The suitability of the regression model was evaluated

using the Hosmer-Lemeshow test. Accordingly, the regression model was considered statistically suitable if the *P* value was <.05. The 95% confidence intervals were calculated for the odds ratios [Exp(B)]. The Wald statistical analysis was conducted to determine the significance of coefficient B.

3 | RESULTS

A total of 197 individuals who had undergone thyroid surgery for DTC participated in this study. There were 117 (59.4%) women and 80 (40.6%) men. The median age was 39 (22-67) years. In MARS, 77 (39.1%) participants scored <20 and were indicated to have low medication adherence, whereas 120 (60.9%) scored ≥20 and were indicated to have high medication adherence. Table 1 shows the descriptive statistics to assess sociodemographic and disease-related characteristics of DTC survivors according

TABLE 2 Psychological factors of thyroid cancer survivors according to medication adherence

Variable	Total n = 197	Low adherence [MARS median score < 20] n = 77	High adherence [MARS median score ≥ 20] n = 120	<i>P</i>
HADs-anxiety	8 (2-19)	9 (2-19)	7 (2-16)	.001
HADs-depression	9 (2-18)	10 (3-18)	9 (2-18)	.012
HADs-total	16 (4-35)	19 (6-35)	15.50 (4-31)	.001
BIPQ				
Consequences	3 (0-7)	4 (0-7)	2 (0-7)	<.001
Timeline	8 (4-10)	8 (4-10)	9 (5-10)	.016
Personal control	8 (3-10)	7 (3-10)	9 (4-10)	<.001
Treatment control	7 (2-10)	6 (2-9)	8 (3-10)	<.001
Identity	3 (0-9)	4 (0-9)	2 (0-7)	<.001
Understanding, concern	4 (0-9)	4 (1-9)	3 (0-8)	<.001
Illness coherence	7 (2-10)	6 (2-10)	8 (3-10)	<.001
Emotional representation	3 (0-8)	4 (0-8)	2.5 (0-7)	<.001
Total	43 (29-56)	44 (29-56)	43 (35-53)	.454
BMQ-specific				
Concerns	2.4 (1-4)	3 (1.4-4)	2.2 (1-3.80)	<.001
Necessity	3.4 (1.6-4.8)	3 (1.6-4.6)	3.8 (1.80-4.80)	<.001
Necessity beliefs (differential)	1.2 (-2.2-3.6)	0 (-2.20-3.20)	1.8 (-1.60-3.60)	<.001
BMQ-general				
Overuse	1.5 (1-3.5)	1.75 (1-3.5)	1.50 (1-2.50)	<.001
Harm	1.75 (1-3.5)	2 (1-3.5)	1.50 (1-2.75)	<.001
BMQ-total score	9.15 (7.4-12.55)	9.5 (7.85-12.55)	9.02 (7.40-11.20)	<.001

Note: Data given as median (min-max); Mann-Whitney *U* test; Values of *P* < 0.05 were accepted as significant and are shown in bold.

Abbreviations: BMQ, Beliefs about Medicines Questionnaire; B-IPQ, Brief Illness Perception Questionnaire; HAD, hospital anxiety and depression scale.

to their medication adherence. There were no significant differences between the adherent and nonadherent groups in terms of disease-related characteristics. Among sociodemographic characteristics, only a low education level (≤ 8 years) and low monthly income (< 5000 TL) were significantly associated with low medication adherence ($P < .001$, $P = .03$, and $P = .001$, respectively).

The results from HAD, B-IPQ and BMQ are shown in Table 2. The HADs-total, HADs-anxiety and HADs-depression scores were significantly higher in the nonadherent group compared to the adherent group ($P = .001$, $P = .012$, and $P = .001$, respectively). Similarly, all items of B-IPQ were significantly related to adherence. The scores in the subscales of consequences, identity, concern and emotional representation were significantly higher in the nonadherent group ($P < .001$, $P < .001$, $P < .001$, and $P < .001$, respectively), whereas the timeline, personal control, treatment control and illness coherence subscores were significantly higher in the adherent group ($P = .016$, $P < .001$, $P < .001$, and $P < .001$, respectively). All subscales on patient beliefs were significantly related to adherence to LT4 treatment. Nonadherent patients had lower scores in the positive statements about medication as measured on the BMQ subscales and vice versa. The BMQ-specific necessity and necessity beliefs scores were found to be statistically significantly higher in the adherent group ($P < .001$ and $P < .001$, respectively), while the specific-concerns scores were significantly higher in the nonadherent group ($P < .001$). The BMQ-general overuse and Harm scores were significantly higher in the nonadherent group ($P < .001$ and $P < .001$, respectively).

Table 3 shows the correlation analyses between the MARS and B-IPQ scores. The MARS score was positively correlated with timeline ($r = .216$, $P = .004$), personal control ($r = .602$, $P < .001$), treatment control ($r = .626$, $P < .001$), and illness coherence ($r = .534$, $P < .001$), and negatively correlated with consequences ($r = -.500$, $P < .001$), identity ($r = -.537$, $P < .001$), concern ($r = -.470$, $P < .001$), and emotions ($r = -.428$, $P < .001$). There was no significant correlation between the MARS score and the total B-IPQ score ($r = -.095$, $P = .104$).

Table 4 demonstrates the correlation analyses between the MARS score and the demographics and disease and mental health-related factors of DTC survivors. MARS was found to be negatively correlated with HADs-total ($r = -.293$, $P = .024$) HADs-anxiety ($r = -.285$, $P = .027$) and HADs-depression ($r = -.242$, $P = .019$). The BMQ-specific-concern ($r = -.458$, $P < .001$), general-overuse ($r = -.403$, $P < .001$), general-harm ($r = -.385$, $P < .001$) and BMQ-total ($r = -.407$, $P < .001$) scores showed an inverse correlation with the MARS score,

whereas a positive correlation was determined with the BMQ-specific necessity score ($r = .431$, $P < .001$).

The multivariable regression analysis revealed that treatment control in cognitive illness perception (B-IPQ item 4) and medication beliefs (BMQ-general harm) were the important predictors of medication adherence (Nagelkerke $R^2 = .458$, Hosmer-Lemeshow test $P = .971$). Higher perception of treatment control over the illness (OR: 0.484, 95% CI: 0.371-0.632) was significantly associated with better medication adherence; however, greater belief concerning medication harmfulness (OR: 3.353, 95% CI: 1.501-7.490) was the only predictor of low adherence (Table 5).

TABLE 3 Correlation coefficients between the MARS Adherence Questionnaire and B-IPQ subscales

B-IPQ	MARS
Consequences	-.500 ^a
Timeline	.216 ^a
Personal control	.602 ^a
Treatment control	.626 ^a
Identity	-.537 ^a
Understanding, concern	-.470 ^a
Illness coherence	.534 ^a
Emotions	-.428 ^a
Total score	-.095

Note: Spearman's correlation test.

Abbreviation: B-IPQ, Brief Illness Perception Questionnaire.

^aCorrelation is significant at the .01 level.

TABLE 4 Correlation coefficients between the MARS Adherence Questionnaire score and the demographic, clinical and psychological variables of thyroid cancer survivors

Variables	MARS
Age, year	-.120
Years since surgery, year	-.014
HADs-anxiety	-.285 ^a
HADs-depression	-.242 ^a
HADs-total	-.293 ^a
BMQ-concern	-.458 ^a
BMQ-necessity	.431 ^a
BMQ-overuse	-.403 ^a
BMQ-harm	-.385 ^a
BMQ-total	-.407 ^a

Note: Spearman's correlation test.

Abbreviations: BMQ, Beliefs about Medicines Questionnaire; HAD, Hospital Anxiety Depression Scale.

^aCorrelation is significant at the .01 level.

	Wald	df	P	Exp(B)	95% CI for Exp(B)	
					Lower	Upper
B-IPQ treatment control	28.554	1	.000	0.484	0.371	0.632
BMQ-general harm	8.708	1	.003	3.353	1.501	7.490
Constant	3.298	1	.069	0.069		

TABLE 5 Regression model for medication adherence

Abbreviations: BMQ, Beliefs about Medicines Questionnaire; B-IPQ, Brief Illness Perception Questionnaire; CI, confidence interval; df, degrees of freedom; Exp(B), odds ratio.

4 | DISCUSSION

Optimal medication adherence has significant implications for patient well-being and effectiveness of therapy. However, even in developed countries, only about half of the population with chronic diseases are estimated to comply with their prescribed medication.²⁰ More than 200 variables have been defined in the literature as influencers of adherence, but no consistent risk profile has yet been identified for nonadherence comprising all chronic conditions.²¹

To the best of our knowledge, this is the first study to report the prevalence of medication adherence in patients under LT4 treatment following single centered-DTC surgery, and to determine the associations between several variables that influence this behavioral pattern.

DTC has a consistently rising incidence rate, with a particularly increased number of cases of papillary thyroid carcinoma and a relatively steady number of follicular thyroid carcinoma over the past three decades. According to the results of preoperative risk assessment, in selected low-risk tumors, smaller than 4 cm without any lymph node metastasis, unilateral lobectomy may be a surgical option with slightly higher local recurrence, while bilateral total thyroidectomy is currently the standard surgical procedure in cases with a slightly increased risk of recurrent laryngeal nerve injury and temporary or permanent hypoparathyroidism.²² There is no consensus over the need for central neck dissection (CND) in patients with unknown lymph node status, and there is no high-level evidence for or against its usefulness for low-risk tumors. There is a reported moderate reduction in central neck recurrence (5%-10%) but no improvement in overall survival in some studies supporting prophylactic CND for low-risk tumors. Since prophylactic CND provides wider information array about lymph node status, including micrometastasis, it may be helpful to estimate prognosis and guide subsequent treatment and follow-up.²³ Exogenous LT4 is a generally accepted treatment for all DTC patients, derived from a wide array of studies and recommended in all guidelines. The two main objectives of this life-long therapy are hormone replacement to correct surgically induced hypothyroidism and

TSH hormone suppression to reduce the rate of recurrence and cancer-related-mortality, especially in high-risk patients.²⁴

LT4 treatment adherence after DTC surgery has priority over other types of hypothyroidism treatment due to its double action effect on the underlying pathology. Each patient is advised to always receive the same preparation in a carefully tailored dosage to ensure the optimal blood thyroid hormone and TSH levels. In some special situations, such as pregnancy, in cases of significant weight gain or loss, or older patients with heart disease, the adjustment of dosage can be required.^{23,24} In the present study, each patient was provided with detailed information about LT4 treatment after surgery before discharge from hospital both verbally and through a booklet.

Medication adherence is an important factor that should be carefully followed up in patients with chronic disease that would require long-lasting treatment. Cancer medication nonadherence has been associated with increased recurrence rates and decreased overall survival. There are many studies in the literature that discuss the adherence to oral medication in patients with cancer, including hematologic malignancies, melanoma, gastrointestinal stromal tumors, lung, prostate, colon, breast, renal cell, and hepatocellular carcinoma, as well as thyroid carcinoma.²⁵⁻²⁹ Due to its double-sided action, medication following thyroid carcinoma differs from the other cancer types in terms of prevention of both hypothyroidism and disease recurrence.

The reported rates of adherence to LT4 treatment widely vary in the literature from 36.8 to 78%, with results depending on the underlying thyroid disease and methodology used for estimating medication adherence.⁴ In the present study, self-reported medication nonadherence was relatively lower (39.1%) compared to previous studies among patients with thyroid cancer. Morris et al reported that 41% of 74 pediatric patients with thyroid cancer were unable to fully adhere to postoperative LT4 treatment.²⁵ In another study conducted with thyroid cancer survivors, Mols et al revealed that 52% of the patients enrolled in the study were medically non-adherent.²⁶ Although self-reported adherence measures are prone to overestimate adherence due to self-

presentation and recall bias, they have the advantage of being an easy, inexpensive and rapid method to apply.^{8,26} Currently, there is no specific self-reported questionnaire for assessing the compliance of patients with thyroid supplementation, but MARS is the most commonly used and reliable self-test in patients treated for hypothyroidism.²⁶

Many factors have been investigated for the predictability of adherence, with the most prominent examples being sociodemographic factors, disease and medication characteristics, perceptions and cognitive representations about illness and medication, and physician-patient relationship. The overview of adherence issues published by WHO recommends a “hand model” to increase the dynamic rates of adherence in a variety of chronic conditions. Like the fingers of a hand, this model has five main components, namely patient, therapy, mental health, health system, and socioeconomic factors.^{8,30} In the current study, we investigated patient-, disease-, and mental health-related factors in DTC survivors.

To date, only one study has addressed some parts of the aforementioned model proposed by WHO among DTC survivors.²⁶ That study reported that younger patients with a higher education level that were more often employed were nonadherent to LT4 therapy at a higher rate. In contrast, in our study, more educated patients with a higher monthly income were more likely to be adherent to treatment, and there was no association between medication adherence and age.²⁶ Disease-related factors (eg, years since surgery, type of surgery, perioperative complications, family history of DTC, frequency of hospital visits, and comorbidities) were found to be not associated with adherence, similar to the previous study. We determined that all variables of B-IPQ (consequences, timeline, personal control, treatment control, identity, concern, illness coherence, and emotions) were significantly related to adherence and correlated with the MARS score. Higher scores on timeline, personal and treatment control and illness coherence were associated with good adherence and correlated with a higher MARS score. In other words, patients with positive beliefs about their life-long therapy, controllability of their illness, and trust in their existing treatment demonstrated good adherence behavior. On the other hand, the negative significant correlation of consequences, identity, concern and emotions with the MARS score was an indicator that the patients who were too concerned about, emotionally affected by or obsessed with every symptom they experienced in relation to their disease tended to show poor adherence. Hirsch et al reported that the illness perception of patients with thyroid cancer was unrelated to the clinical severity of their disease. They recommended that this higher correlation in emotional representations could be overcome by providing patients with more information

and support immediately after surgery and designing cognitive behavioral interventions to improve the illness perception of the targeted population.³¹

A new finding obtained from this study was that the anxiety and depression scores were significantly higher in the nonadherent group, advocating previous results indicating emotional stress as an important factor determining LT4 adherence.³² A recently published study revealed that health-related quality of life in patients with thyroid cancer was negatively influenced by impaired psychological and emotional well-being due to anxiety, depression, and fatigue.³³ Roberts et al reported that DTC survivors, even those with normal TSH levels and euthyroid state felt that they had missing or inadequate knowledge of lifestyle factors affecting recurrence, negative consequences, symptoms of recurrence, and importance and side effects of medication.³⁴ Disease-free patients with a history of DTC treated with TSH-suppressive doses of LT4 often experience potential psychological adverse effects of thyroid hormone excess, and consequently show poor compliance with their treatment.³⁵ On the other hand, the association between subclinical hypothyroidism and impaired psychological well-being has been demonstrated in many studies to be associated with poor medication adherence, but this hypothesis also includes an apparent paradox that creates “a cycle of misattribution” with the lack of improvement of depressive symptoms and medication compliance even when patients are on thyroxine substitution.^{31,32,36} Based on these data, we can conclude that not hormonal imbalance but the disease itself is the leading point addressing to anxiety and depression, which determines adherence to LT4 medication.

Medication beliefs have been shown to directly influence patients' attitudes toward self-management in chronic diseases requiring life-long drug treatment. However, little is known about patient preferences regarding the benefits and harms of LT4 treatment. In the present study, positive beliefs in medication necessity were significantly associated with a higher adherence rate and correlated with a higher MARS score. In contrast, specific concerns about potential adverse effects and general statements about the overuse or harmfulness of LT4 treatment were significantly associated with non-adherence in our patient group and were also negatively correlated with the MARS score. These results show great parallelism with other studies addressing adherence to oral medications after various cancer survivorship. Non-adherence to oral hormone therapy for cancer treatment has been attributed to irrational medication-related beliefs in most cases.^{27,37} Although the superiority of recurrence-preventive effects of LT4 treatment in DTC is debatable in the properly surveilled low-risk patient

group in recent guidelines,³⁸ the association between thyroid hormone suppression therapy and reduction in major adverse clinical events, namely disease progression/recurrence and death was indicated in a meta-analysis.³⁹ Therefore, patient education concerning both thyroid hormone supplementation and medical preventive measures that should be taken after DTC surgery seems to be a good strategy to increase medication adherence especially in patient groups presenting with medication misbeliefs related to the usefulness or harmfulness of therapy.

The drivers of nonadherence are complex, but the present study revealed that the primary influencer and predictor of high adherence in DTC survivors was patients' confidence in available treatment, and for low adherence, possible harmful effects constituted the primary predictor. This is an important result showing that physicians that provide long-term follow-up of DTC survivors should spend more time assessing these patients in terms of psychosocial factors that may affect their compliance with the use of their existing medication.

This study has certain limitations. First, while self-reported questionnaires are the most commonly used methods to measure adherence, there is also concern that individuals can overreport their level of adherence; thus, they may give some misleading information about adherence. Second, we did not have any information about the thyroid hormone status of the patients, which may have caused a bias in psychological terms in case of hypothyroidism or hyperthyroidism. On the other hand, the relatively large size of the study population who had been previously well informed about their disease and treatment and the enthusiasm of the patients to participate in the study (no drop-out) are among the strengths of the study.

In conclusion, we found a higher medication adherence rate to LT4 treatment among DTC survivors when compared to the literature. We attributed this result to the better educational programs applied for this specific patient group immediately after surgery. We determined that having greater confidence in treatment modality and greater belief that the medication had minimum risk of harm, were the most important predictors of higher adherence to LT4 in Turkish patients with a DTC history. Our findings indicate that special attention should be paid to less-educated patients with low socioeconomic status, and a well-designed and simplified illness perception and treatment belief program should be provided for each patient.

Supporting patients' perceptions of control and reliability of LT4 treatment should be the main targets in efforts to increase medication adherence in DTC survivors. The implementation of educational programs addressing the effectiveness and low risk of harm of

prescribed medication can minimize nonadherence, and consequently reduce thyroid hormonal imbalance and possible recurrences.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

Pelin Basım: concept, design, supervision, resources, data collection and/or processing, education and follow-ups, analysis and/or interpretation, literature search, writing manuscript, critical review; **Derya Argun:** design, resources, writing manuscript; **Yaşar Özdenkaya:** data collection and/or processing; education and follow-ups.

ETHICS STATEMENT

Ethics committee approval was received for this study from the Research Ethics Committee of Medipol University (10840098-604.01.01-E.41155 decision number: 609).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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