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Thyroid-Stimulating Hormone Suppression Therapy and Its Association with Anxiety, Depression, Hypomania, and Quality of Life in Differentiated Thyroid Cancer

ABSTRACT

Objective: This study aimed to investigate the impact of thyroid-stimulating hormone (TSH) suppression therapy on psychological outcomes and quality of life in patients with differentiated thyroid carcinoma (DTC), with particular focus on anxiety, depression, hypomania, and related hormonal parameters.

Methods: A total of 87 adult patients with DTC receiving levothyroxine therapy were evaluated. Participants were grouped according to their TSH levels: <0.1, 0.1-0.5, and 0.6-4.2 mIU/L. Psychometric evaluations included the Beck Anxiety Inventory, Beck Depression Inventory, Hypomania Checklist-32, and Quality of Life Short Form (SF-36) Quality of Life Scale. Thyroid function tests and clinical parameters were recorded. Comparative, correlational, and multivariable regression analyses were performed.

Results: No significant differences were found in psychometric scores or SF-36 subdomains among the TSH-based groups. However, a weak positive correlation was identified between TSH levels and anxiety scores ($r = 0.175$, $P = .044$), while T3 levels were inversely correlated with depression scores ($r = -0.216$, $P = .045$). These exploratory associations did not remain statistically significant in multivariable linear and logistic regression analyses. No independent associations were identified between TSH categories or thyroid hormone levels and psychological outcomes.

Conclusion: The TSH suppression therapy does not appear to significantly affect quality of life or mood-related symptoms in a categorical manner. Although these associations were attenuated in regression analyses, subtle relationships among TSH, T3, and psychological parameters may still exist, suggesting that psychological outcomes are influenced by multiple clinical and psychosocial factors. These findings support the need for individualized treatment strategies that consider both oncologic control and patient well-being.

Keywords: Anxiety, depression, levothyroxine, quality of life, thyroid neoplasms

Introduction

Based on GLOBOCAN 2020 estimates, thyroid cancer represents one of the most common endocrine malignancies and is the ninth most frequently diagnosed cancer worldwide.[1] Thyroid neoplasms arise from different cell lineages, although most cases belong to the differentiated thyroid carcinoma (DTC) group, including papillary, follicular, oncocytic, and invasive encapsulated follicular variants.[2]

While active surveillance has recently gained traction for low-risk PTCs, surgery remains the cornerstone of treatment for DTC.[3,4] Postoperative management involves staging, assessment for radioactive iodine (RAI) therapy, and decisions regarding the degree of thyroid-stimulating hormone (TSH) suppression via levothyroxine therapy.[3] Suppressive levothyroxine treatment plays a central role in minimizing tumor regrowth by lowering TSH levels, yet its physiological consequences must not be overlooked.[3] Long-term TSH suppression may lead to systemic adverse effects, particularly reductions in bone mineral density and deterioration of cardiovascular function.[5,6]

Beyond these somatic risks, the psychological and cognitive implications of chronic TSH suppression have also drawn attention. Several studies have suggested that subclinical hyperthyroidism may negatively influence mood, quality of life, and cognitive performance.[7,8] Previous studies have also suggested links between hyperthyroid states and mood dysregulation,

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including manifestations within the bipolar spectrum such as hypomanic symptoms.[9,10]

Therefore, this study was designed to examine the potential psychological consequences of levothyroxine-mediated TSH suppression in patients with DTC, focusing on anxiety, depression, hypomanic symptoms, and overall quality of life.

Methods

Study Oversight

The study was carried out at a tertiary referral endocrinology center affiliated with an academic institution. The study protocol was approved by the institutional ethics committee of İstanbul University-Cerrahpaşa Faculty of Medicine (Approval No: E-83045809-604.01.01-743902; Date: August 1, 2023), and all procedures were conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from every participant before enrollment. This study was observational and non-interventional; therefore, clinical trial registration was not required.

Participants

Adult individuals with a diagnosis of DTC who attended the outpatient clinic between August 2023 and January 2024 were consecutively recruited. Patients were excluded if they were illiterate, had a history of psychiatric illness, had been diagnosed with non-thyroidal malignancies, used antidepressant or anxiolytic medications, had a history of substance or alcohol dependence, were bedridden, had experienced head trauma, or declined to participate. Following the exclusion process, 92 eligible participants remained for initial evaluation. Five additional patients with TSH concentrations exceeding the upper reference range (>4.2 μIU/mL) were excluded, leaving 87 individuals for the final analyses.

Information such as demographic data, comorbidities, medications, educational status, and monthly income level was obtained from the patients. Recorded comorbidities were limited to common chronic conditions, including diabetes mellitus, hypertension, hyperlipidemia, and asthma. Parameters such as duration of thyroid cancer, status of RAI treatment, cancer staging, presence of recurrence, and weekly levothyroxine dose were recorded.

Blood samples and psychometric assessments were performed on the same day during routine outpatient visits. Laboratory tests were obtained in the morning after an overnight fast, and psychometric questionnaires were completed on the same visit. Serum thyroid function tests were measured using commercial kits on a Cobas c702 automated chemistry analyzer (Roche Diagnostics GmbH, Mannheim, Germany), according to the manufacturer's instructions.

The reference ranges were as follows: TSH, 0.27-4.2 μIU/mL; free triiodothyronine, 2.0-4.4 pg/mL; and free thyroxine, 0.93-1.7 ng/dL.

Patients were categorized into 3 groups according to their TSH levels: suppressed TSH (<0.1 mIU/L), mildly suppressed TSH (0.1-0.5 mIU/L), and non-suppressed TSH (0.6-4.2 mIU/L), based on commonly used clinical targets for TSH suppression therapy in DTC.

Psychometric Assessments

Participants completed a battery of validated self-report instruments to assess psychological status and quality of life:

- **Quality of Life Short Form (SF-36):** A 36-item scale covering 8 subdomains, including physical functioning, mental health, and social functioning. Total scores range from 0 to 100, with higher scores indicating better quality of life.[11,12] The Turkish version was validated by Kocyigit et al.[13]
- **Hypomania Checklist (HCL-32):** Comprising 32 yes/no items and one Likert-style item evaluating mood elevation, this instrument screens for hypomanic symptoms.[14] The Turkish adaptation was validated by Vahip et al[15] in 2017.
- **Beck Depression Inventory (BDI):** This 21-item scale assesses the severity of depressive symptoms, with each item scored from 0 to 3, yielding a total score range of 0 to 63.[16] The Turkish adaptation was validated by Hisli N et al.[17]
- **Beck Anxiety Inventory (BAI):** Composed of 21 items, each rated on a 0-3 scale, the BAI measures the intensity of anxiety symptoms.[18] The Turkish adaptation was validated by Ulusoy et al.[19]

All psychometric tools were selected in consultation with psychiatrists experienced in endocrine-related mood disturbances.

Statistical Analysis

Statistical analyses were conducted using IBM Statistical Package for the Social Sciences Statistics, version 22.0 (IBM SPSS Corp.; Armonk, NY, USA). Distributional assumptions were evaluated using the Shapiro–Wilk test, along with graphical assessments of histograms and Q-Q plots. Equality of variances was examined with Levene's test. Continuous variables are reported as mean ± SD or median (IQR), whereas categorical variables are presented as counts and percentages.

Group comparisons were performed using one-way analysis of variance or Kruskal–Wallis test with Bonferroni correction, independent samples *t*-test or Mann–Whitney *U*-test, and chi-square or Fisher's exact test, as appropriate. Correlations were assessed using Pearson's or Spearman's coefficients. A two-sided $P < .05$ was considered statistically significant.

Multivariable linear regression analyses were performed to evaluate associations between TSH groups and psychological outcomes, adjusting for age, sex, marital status, disease duration, levothyroxine dose, RAI treatment, recurrence, and presence of chronic

MAIN POINTS

- TSH suppression therapy was not associated with significant differences in anxiety, depression, hypomania, or health-related quality of life among patients with differentiated thyroid carcinoma across TSH-defined groups.
- The degree of TSH suppression was not associated with clinically meaningful differences in psychometric outcomes.
- Weak exploratory correlations were observed between TSH and anxiety and between serum T3 level and depression; however, these associations were not significant after adjustment for potential confounders.
- These findings suggest that psychological well-being in long-term survivors of differentiated thyroid carcinoma is influenced by factors beyond thyroid hormone suppression alone.
- The findings support comprehensive follow-up that incorporates patient-reported outcomes alongside oncologic management.

disease; serum T3 was additionally included in the depression model. Covariates were selected a priori based on clinical relevance and their potential to confound psychological outcomes in patients with DTC. Multivariable logistic regression analyses were also conducted using binary outcomes based on validated cut-off values, with the TSH group entered as a dummy variable and the suppressed TSH group (<0.1 mIU/L) as the reference.

Because this was an observational study that included all eligible patients during the study period, no formal sample size calculation was performed. Consequently, the study may have had limited power to detect small effect sizes, and non-significant findings should be interpreted cautiously.

Results

A total of 87 patients were included in the study, comprising 66 women (75.9%) and 21 men (24.81%). Based on TSH levels, participants were categorized into 3 groups: group 1 (TSH < 0.1 mIU/L), group 2 (TSH between 0.1 and 0.5 mIU/L), and group 3 (TSH between 0.6 and 4.2 mIU/L). Demographic factors such as age, sex, educational attainment, and income level were comparable across the 3 groups (Table 1).

A statistically significant difference emerged in the median disease duration: 5 [3-7] years in group 1, 6 [5-12] years in group 2, and 10 [5.5-16] years in group 3 ($P = .006$). Post hoc testing identified a significant difference between groups 1 and 3 ($P = 0.004$). Weekly levothyroxine doses also showed significant variability ($P = .009$), with Group 1 receiving 950 µg/week (800–1050), Group 2 receiving 900 µg/week (800–1050), and Group 3 receiving 700 µg/week (625–950). Pairwise analysis indicated a significant contrast between Groups 1 and 3 ($P = 0.012$).

As expected, median TSH levels differed significantly between all groups: 0.04 mIU/L [0.018–0.06] in Group 1, 0.25 mIU/L [0.17–0.33] in Group 2, and 1.82 mIU/L [1.22–3.19] in group 3 ($P < .001$). No significant differences were found in thyroglobulin levels between groups. Mean serum T3 levels were significantly lower in group 3 (2.6 ± 0.37 mIU/L) compared to group 1 (2.95 ± 0.66 mIU/L) ($P = .007$; pairwise $P = .002$). A downward trend in T4 levels was also noted: 1.71 ± 0.4 mIU/L in group 1, 1.65 ± 0.24 mIU/L in group 2, and 1.39 ± 0.24 mIU/L in group 3 ($P < .001$), with post-hoc differences between groups 1 and 3 ($P = .002$) and groups 2 and 3 ($P = .001$).

The proportion of patients receiving RAI treatment did not differ significantly among groups (group 1: 70.4%, group 2: 80.6%, group 3: 58.6%; $P = .176$). Similarly, cancer stage distribution was comparable across groups. However, recurrence rates varied significantly: 3 patients (11.5%) in group 1 and 8 patients (27.6%) in group 2, with no recurrences in group 3 ($P = .012$; group 2 vs. 3, $P = .005$).

Table 1. Demographic Characteristics of the Patients

	Group 1 (n = 27)	Group 2 (n = 31)	Group 3 (n = 29)	*P*
Age, year, mean ± SD	46.1 ± 10.1	49.4 ± 12.9	50.4 ± 11.7	.333
Gender				.224
Female, n (%)	18 (66.7)	23 (74.2)	25 (86.2)	
Male, n (%)	9 (33.3)	8 (25.8)	4 (13.8)	
Marital status				.005
Married, n (%)	21 (77.8)	31 (100)	20 (69)	
Single, n (%)	6 (22.2)	0 (0)	9 (31)	
Comorbidity, n (%)	16 (59.3)	13 (41.9)	18 (62.1)	.237
Income				.586
Below minimum wage, n (%)	9 (33.3)	11 (35.5)	8 (27.5)	
Above minimum wage, n (%)	18 (66.7)	20 (64.5)	21 (72.5)	
Smoker, n (%)	0 (0)	1 (3.2)	1 (3.4)	.630

Table 2. Comparison of Laboratory Parameters, Recurrence, and Stage Between Groups

	Group 1 (n = 27)	Group 2 (n = 31)	Group 3 (n = 29)	*P*
Disease duration, year, median [IQR]	5 [3-7]	6 [5-12]	10 [5.5-16]	**.006**[a]
Lt4 dose, µg/week, median [IQR]	950 [800-1050]	900 [800-1050]	700 [625-950]	**.009**[b]
TSH, mIU/L, median [IQR]	0.04 [0.01-0.06]	0.25 [0.17-0.33]	1.82 [1.22-3.19]	**<.001**[c]
Tg, mIU/L, median [IQR]	0.04 [0.04-0.10]	0.04 [0.04-0.04]	0.04 [0.04-0.27]	.298
Anti Tg, mIU/L, median [IQR]	15.2 [12.7-19.8]	17.8 [14.2-23.9]	14.8 [13.3-17.8]	.105
T3, mIU/L, mean ± std	2.95 ± 0.66	2.76 ± 0.42	2.6 ± 0.37	**.007**[d]
T4, mIU/L, mean ± std	1.71 ± 0.4	1.65 ± 0.24	1.39 ± 0.24	**<.001**[e]
Receiving RAI treatment (%)	19 (70.4)	25 (80.6)	17 (58.6)	.176
Stage, (%)				.392
Stage 1, n (%)	12 (46.2)	11 (40.7)	17 (70.8)	
Stage 2, n (%)	5 (19.2)	6 (22.2)	2 (8.3)	
Stage 3, n (%)	5 (19.2)	5 (18.5)	4 (16.7)	
Stage 4, n (%)	4 (15.4)	5 (18.5)	1 (4.2)	
Presence of recurrence, n (%)	3 (11.5)	8 (27.6)	0 (0)	**.012**[f]

IQR, interquartile range; LT4, levothyroxine; RAI, radioactive iodine; SD, standard deviation; Tg, thyroglobulin.
[a]Difference between groups 1 and 3 ($P = .004$).
[b]Difference between groups 1 and 3 ($P = .012$).
[c]Difference among all groups ($P < .001$).
[d]Difference between groups 1 and 3 ($P = .002$).
[e]Difference between groups 1 and 3 ($P < .001$) and between groups 2 and 3 ($P = .001$).
[f]Difference between groups 2 and 3 ($P = .005$).

Table 3. Comparison of Groups in Terms of Depression, Anxiety, Hypomania, and Quality of Life: Scale Scores and Presence of Symptoms

	Group 1 (n: 27)	Group 2 (n: 31)	Group 3 (n: 29)	*P*
Beck Anxiety Score, n, median [IQR]	10 [6-23]	14 [6-23]	16 [9-26.5]	.324
Beck Depression Score, n, median [IQR]	12 [5 -15]	11 [6-18]	15 [4-21]	.745
Hypomania score, n, median [IQR]	17 [15-22]	17 [14-22]	18 [13-22]	.998
Physical function, n, median [IQR]	80 [55-90]	75 [60-95]	70 [50-85]	.591
Physical role limitations, n, median [IQR]	75 [25-100]	50 [0-100]	50 [25-75]	.455
Pain, mean ± SD	63.05 ± 31.2	60.56 ± 29.2	62.7 ± 24.4	.863
General health perception, n, median [IQR]	55 [35-75]	60 [35-70]	55 [35-77.5]	.928
Vitality, n, mean ± SD	52.04 ± 21.5	48.39 ± 19.2	49.1 ± 22.2	.698
Social function, n, median [IQR]	80 [55-90]	75 [50-100]	75 [50-100]	.941
Emotional role limitations, n, median [IQR]	33.3 [33.3-66.6]	66.6 [33.3-100]	66.6 [33.3-66.6]	.583
Mental health, n, median [IQR]	68 [52 - 76]	64 [56-76]	64 [52-80]	.919
Presence of anxiety, n (%)	12 (44.4)	17 (54.8)	16 (55.2)	.660
Presence of depression, n (%)	4 (14.8)	9 (29)	12 (41.4)	.090
Presence of hypomania, n (%)	23 (85.2)	24 (77.4)	21 (72.4)	.509

IQR, interquartile range; SD, standard deviation.

The evaluation between the groups in terms of laboratory parameters, recurrence, and stage is summarized in Table 2.

Across the 3 TSH-level groups, no significant variation emerged in psychometric outcomes (BAI, BDI, HCL-32, SF-36 subdomains) (Table 3). Similarly, anxiety, depression, and hypomania prevalence did not differ significantly: anxiety in 44.4% (group 1), 54.8% (group 2), 55.2% (group 3) ($P=0.666$); depression in 14.8%, 29%, and 41.4% respectively ($P=.090$); and hypomania in 85.2%, 77.4%, and 72.4% ($P=.509$) (Table 3).

Stratifying by RAI treatment revealed no significant differences in anxiety, depression, hypomania severity, or overall quality of life scores (Table 4).

Stratification according to cancer stage (I-IV) also did not reveal any significant differences in psychological outcomes. Anxiety, depression, and hypomania scores were comparable across stages ($P=.542$, $P=.484$, and $P=.334$, respectively). Similarly, no significant differences were observed in quality-of-life measures across stages, including physical functioning, role limitations, emotional well-being, vitality, mental health, social functioning, and pain (all $P>.05$).

Correlation analysis identified a weak yet statistically significant positive association between TSH and anxiety scores ($r=0.175$, $P=.044$), and an inverse association between T3 and depression scores ($r=-0.216$, $P=.045$) (Table 5). Given the number of outcomes evaluated and the borderline statistical significance, these findings should be interpreted as exploratory.

Multivariable Linear Regression Analyses

To determine whether TSH suppression status was independently associated with psychological outcomes, adjusted linear regression models were constructed that incorporated demographic and disease-related covariates, including age, sex, marital status, disease

Table 4. Comparison of Patients with and Without RAI Treatment in Terms of Depression, Anxiety, Hypomania, and Quality of Life: Scale Scores and Presence of Symptoms

	Receiving RAI Treatment (n: 61)	Not Receiving RAI Treatment (n: 26)	*P*
Beck Anxiety Score, n, median [IQR]	15 [7.5-24]	10 [6.7-22.2]	.653
Beck Depression Score, n, median [IQR]	12 [5-17.5]	11 [4-18.5]	.915
Hypomania score, n, median [IQR]	18 [15-21.5]	15.5 [13-22]	.519
Physical function, n, median [IQR]	75 [55-85]	85 [53.7-95]	.390
Physical role limitations, n, median [IQR]	50 [0-75]	62.5 [25-100]	.189
Pain, mean ± SD	62.3 ± 28.3	61.4 ± 28.1	.830
General health perception, n, median [IQR]	60 [35-72.5]	57.5 [33.7-75]	.996
Vitality, n, mean ± SD	50.5 ± 19.8	48.1 ± 23.4	.635
Social function, n, median [IQR]	77.5 [48.7-100]	77.5 [53.7-92.5]	.910
Emotional role limitations, n, median [IQR]	66.6 [33.3-66.6]	66.6 [33.3-75]	.652
Mental Health, n, median [IQR]	68 [56-76]	62 [48-76]	.322
Presence of anxiety n (%)	33 (54.1)	12 (46.2)	.497
Presence of depression n (%)	17 (27.9)	8 (30.8)	.784
Presence of hypomania n (%)	49 (80.3)	19 (73.1)	.454
std: standard deviation, IQR: interquartile range	std: standard deviation, IQR: interquartile range	std: standard deviation, IQR: interquartile range	std: standard deviation, IQR: interquartile range

Table 5. Correlations of Disease Duration, LT4 Dose, Age, TSH, T3, and T4 with Depression, Anxiety, Hypomania, and Quality of Life Scores

	Anxiety Score	Depression Score	Hypomania Score	Physical Function	Physical Role Limitation	Emotional Role Limitation	Vitality	Mental Health	Social Function	Pain	General Health Perception
LT4 dose	$r = -0.110$ $P = .310$	$r = -0.153$ $P = .157$	$r = 0.106$ $P = .329$	$r = 0.139$ $P = .200$	$r = 0.152$ $P = .159$	$r = 0.094$ $P = .387$	$r = 0.109$ $P = .317$	$r = -0.099$ $P = .364$	$r = 0.066$ $P = .543$	$r = 0.053$ $P = .627$	$r = 0.125$ $P = .248$
Disease duration	$r = 0.041$ $P = .708$	$r = 0.021$ $P = .849$	$r = 0.056$ $P = .607$	$r = -0.181$ $P = .093$	**$r = -0.233$** **$P = .030$**	$r = -0.088$ $P = .417$	$r = 0.036$ $P = .743$	**$r = 0.230$** **$P = .032$**	$r = -0.014$ $P = .900$	$r = -0.139$ $P = .200$	$r = -0.184$ $P = .087$
Age	$r = -0.026$ $P = .813$	$r = -0.047$ $P = .664$	$r = -0.059$ $P = .587$	**$r = -0.214$** **$P = .047$**	$r = -0.197$ $P = .067$	$r = -0.176$ $P = .102$	$r = 0.112$ $P = .304$	$r = 0.174$ $P = .107$	$r = 0.018$ $P = .866$	$r = -0.034$ $P = .757$	$r = -0.092$ $P = .397$
T3	$r = -0.130$ $P = .232$	**$r = -0.216$** **$P = .045$**	$r = 0.118$ $P = .276$	$r = 0.058$ $P = .596$	$r = 0.097$ $P = .373$	$r = 0.055$ $P = .611$	$r = 0.032$ $P = .768$	$r = -0.049$ $P = .649$	$r = 0.014$ $P = .897$	$r = 0.103$ $P = .344$	$r = 0.088$ $P = .418$
T4	$r = -0.149$ $P = .169$	$r = -0.088$ $P = .417$	$r = -0.038$ $P = .725$	$r = 0.075$ $P = .488$	$r = 0.043$ $P = .694$	$r = 0.019$ $P = .864$	$r = 0.011$ $P = .922$	$r = 0.147$ $P = .174$	$r = 0.043$ $P = .692$	$r = -0.036$ $P = .737$	$r = 0.050$ $P = .643$
TSH	**$r = 0.175$** **$P = .044$**	$r = 0.165$ $P = .127$	$r = -0.019$ $P = .859$	$r = -0.131$ $P = .226$	$r = -0.056$ $P = .605$	$r = 0.025$ $P = .816$	$r = -0.095$ $P = .384$	$r = -0.005$ $P = .960$	$r = -0.009$ $P = .932$	$r = -0.062$ $P = .571$	$r = -0.052$ $P = .634$

LT4, levothyroxine.

duration, levothyroxine dose, RAI treatment, recurrence status, and the presence of chronic disease.

The TSH group was not independently associated with hypomania scores. Neither the moderately suppressed group (TSH_G2: B = −0.442, $P = .787$, 95% CI: −3.684 to 2.800) nor the non-suppressed group (TSH_G3: B = −0.459, $P = .796$, 95% CI: −3.990 to 3.072) differed significantly from the reference group (TSH < 0.1 mIU/L). Among covariates, only chronic disease was significantly associated with hypomania scores (B = −2.715, $P = .045$, 95% CI: −5.368 to −0.063); the overall model was not statistically significant (F = 1.038, $P = .419$; adjusted $r^2 = 0.004$).

The TSH group was similarly not independently associated with anxiety scores (TSH_G2: B = 0.833, $P = .801$, 95% CI: −5.719 to 7.386; TSH_G3: B = 1.507, $P = .675$, 95% CI: −5.630 to 8.643), and no covariates reached significance ($F = 1.319$, $P = .243$; adjusted $r^2 = 0.035$).

For depression, the TSH group was again not independently associated with outcomes (TSH_G2: B = 1.754, $P = .510$, 95% CI: −3.527 to 7.035; TSH_G3: B = −1.368, $P = .637$, 95% CI: −7.119 to 4.383). Male sex was the only significant covariate (B = −6.581, $P = .016$, 95% CI: −11.903 to −1.259); the overall model was not statistically significant (F = 1.614, $P = .128$; adjusted $r^2 = 0.065$). In the extended model, additionally including serum T3, the overall model remained non-significant (F = 1.695, $P = .099$; adjusted $r^2 = 0.081$), and T3 was not independently associated with depression scores (B = −3.111, $P = .144$, 95% CI: −7.313 to 1.091).

Regression diagnostics indicated no major violations of assumptions, with normally distributed residuals, no evidence of heteroscedasticity, and no significant multicollinearity (all VIF values <2).

Multivariable Logistic Regression Analyses

Additional analyses using binary psychological outcomes were conducted to explore whether TSH suppression status was associated with the presence of anxiety, depression, or hypomania according to established cut-off values. For anxiety, the overall model was not statistically significant ($\chi^2 = 4.929$, $P = .553$), and none of the included variables were independently associated with anxiety (e.g., TSH group 2: OR = 1.352, 95% CI: 0.446-4.101, $P = .594$; TSH group 3: OR = 1.146, 95% CI: 0.362-3.626, $P = .817$). For depression, the model approached but did not reach statistical significance ($\chi^2 = 12.450$, $P = .053$, Nagelkerke $r^2 = 0.191$), and no independent predictors were identified (TSH group 2: OR = 2.593, 95% CI: 0.623-10.792, $P = .190$; TSH group 3: OR = 2.721, 95% CI: 0.673-11.002, $P = .160$). No independent predictors were identified. Similarly, for hypomania, the logistic regression model was not statistically significant ($\chi^2 = 7.166$, $P = .306$), and no independent predictors were identified (TSH group 2: OR = 0.464, 95% CI: 0.110-1.958, $P = .296$; TSH group 3: OR = 0.435, 95% CI: 0.100-1.899, $P = .268$). Across all models, TSH categories, age, marital status, and disease duration were not significantly associated with the presence of psychological outcomes after adjustment. Model calibration was adequate for all 3 models, as indicated by non-significant Hosmer-Lemeshow test results (anxiety: $\chi^2 = 6.045$, $P = .642$; depression: $\chi^2 = 9.911$, $P = .271$; hypomania: $\chi^2 = 8.229$, $P = .411$).

Discussion

This study examined whether TSH suppression via levothyroxine influences psychological status; specifically, anxiety, depression,

hypomania, and health-related quality of life in patients with DTC. While group comparisons did not reveal significant differences in psychometric scores or quality of life measures, correlation analyses suggested weak associations between higher TSH levels and increased anxiety, and between lower T3 levels and higher depression scores. In multivariable analyses adjusting for relevant clinical and sociodemographic factors, these associations were attenuated and did not reach statistical significance. Neither TSH categories nor serum T3 levels showed statistically significant independent associations with psychological outcomes in the adjusted models. Similarly, logistic regression analyses using categorical definitions of these outcomes yielded consistent findings. Taken together, these findings suggest that the weak associations observed in unadjusted analyses should be considered exploratory and may be influenced by multiple interacting clinical and psychosocial factors, rather than reflecting strong independent effects of thyroid function parameters alone.

Prior evidence suggests that thyroid dysfunction frequently coincides with mental health disturbances, including heightened rates of depression and anxiety disorders.[20] Not only overt but also subclinical hypothyroidism and hyperthyroidism are thought to have similar effects. Apart from studies underlining a strong relationship between subclinical hypothyroidism and depressive symptoms, there are also studies showing that subclinical hypothyroidism and subclinical hyperthyroidism increase anxiety levels.[21,22] In the present study, the lack of significant group differences in anxiety and depression scores may be explained by the fact that participants understood their subclinical hyperthyroid state as a deliberate part of their treatment strategy. Similarly, the positive correlation between TSH levels and anxiety scores may be explained by this treatment-related perception of disease control, further supporting the overall findings.

Beyond TSH, the analysis also explored the role of peripheral thyroid hormones. The observed inverse correlation between T3 levels and depression aligns with previous research indicating that reduced T3 may be associated with depressive symptomatology.[23] In a study conducted on mice with thyroid hormone receptor alpha 1 mutation, it was observed that depressive behaviors increased in these mice, and these behaviors improved with continuous T3 administration.[24] Based on these data, it is recommended that patients with depression be screened for thyroid dysfunction, but the use of thyroid hormones as adjunctive therapy needs to be further investigated. Furthermore, the fact that this negative correlation does not remain significant in adjusted models suggests that circulating T3 levels may not independently influence the severity of depressive symptoms.

When examining the relationship between thyroid disorders and quality of life, the literature presents inconsistent findings. Some studies report that thyroid dysfunction, even in its subclinical form, adversely affects quality of life. For instance, De Oliveira Chachamovitz et al[25] found that subclinical hyperthyroidism was associated with significantly worse quality of life compared to the euthyroid state. Similarly, in a study carried out by Kırnap et al[26] in patients with DTC, it was shown that the subclinical hyperthyroidism group scored significantly lower in all scales of the SF-36 quality of life survey compared to the euthyroid group. On the other hand, studies consistent with the findings have reported no significant differences in quality of life between individuals with thyroid dysfunction and healthy controls.[27,28] In a study undertaken by Bell et al,[27] no significant differences were found in quality of life scores between 52 patients with subclinical hyperthyroidism and 156 euthyroid individuals. These contrasting results suggest that quality of life may not solely be determined by thyroid function status but may also be shaped by various other individual and psychosocial factors.

In this study, quality of life was comparable across groups, and TSH levels appeared unrelated to it. The literature offers mixed findings on this issue. Among 208 DTC patients evaluated by Monzani et al., those with TSH values exceeding the reference range had the most reduced QoL scores.[29] This was thought to be related to LT4 deprivation and recent diagnosis of malignancy. The best quality-of-life score was observed in the group with effectively suppressed TSH levels, which was explained by a sense of completion of cancer treatment.[29] Conversely, Missaoui et al[30] found that suppressed TSH was linked to poorer psychological and social functioning. Longitudinal findings from Julia Winter et al. further demonstrated that while physical quality of life remained stable over time, mental well-being gradually improved independent of TSH levels.[31] Similarly, the findings indicate that changes in physical or mental quality of life cannot be solely explained by TSH suppression, underscoring the multifactorial nature of psychological adaptation in DTC survivors.

Psychiatric disorders such as mania and psychosis are recognized manifestations of hyperthyroidism, and thyrotoxicosis can rarely present with psychotic or manic symptoms as the initial clinical picture.[32,33] Hyperthyroidism was identified in 7.5% and subclinical hyperthyroidism in 5% of patients presenting with a first episode of mania in one study.[9] In another study, 343 patients with schizophrenia spectrum disorder were evaluated in terms of thyroid dysfunction, and thyrotoxicosis was found in 3% of these patients, while hypothyroidism was shown in 23%.[34] Furthermore, population-based data from Taiwan involving over 21 000 individuals suggested that hyperthyroidism may be associated with an increased risk of developing bipolar disorder.[35] In this study, no significant association was found between levothyroxine-induced TSH suppression and hypomanic symptoms across all analytical approaches, including group comparisons and correlation analyses. The consistent null findings across methods support the conclusions, though sample size and restriction to DTC patients may limit generalizability.

Several limitations should be acknowledged when interpreting the findings. First, the available sample size may have limited the ability to detect modest associations, particularly for smaller effect sizes; consequently, statistically non-significant results should not be interpreted as evidence of the absence of a relationship. In addition, given the number of adjustment variables included in the multivariable analyses, some degree of model instability and overfitting cannot be excluded.

The absence of a healthy control group limits comparisons with the general population, and restriction to DTC patients reduces generalizability. Although comorbidities, cancer stage, and treatment-related variables were recorded, detailed stratification by severity and dynamic risk classification was not consistently available, limiting assessment of their differential impact on psychological outcomes.

Finally, the single-center cross-sectional design does not allow temporal or causal relationships to be established. In addition, the use of self-administered questionnaires may have introduced reporting bias, and residual confounding remains possible. Larger prospective studies with broader clinical characterization are warranted to better define these associations.

In this study, no significant differences were observed in anxiety, depression, hypomania, or quality-of-life scores across TSH-based groups. Although exploratory correlation analyses suggested modest associations between higher TSH and increased anxiety, and between lower T3 and higher depression, these relationships did not remain significant after adjustment. Overall, the findings do not provide statistically significant evidence that psychological outcomes in patients with DTC are independently determined by thyroid hormone suppression within the therapeutic range; rather, they reflect a complex interplay of clinical and psychosocial factors. Although a clear psychological impact was not demonstrated, avoiding unnecessary TSH suppression remains important given known cardiovascular and skeletal risks, supporting an individualized treatment approach.

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

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