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The "Non-Treated" Versus "LT3-Treated" Protocols of Short-Term Hypothyroidism Induction in Differentiated Thyroid Cancer: An Analysis of Hypothyroid Complications, Mood Disorders, and Quality of Life

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ABSTRACT

This study aimed to compare "non-treated" versus "levotriiodothyronine (LT3)-treated" protocols of short-term hypothyroidism induction prior to radioactive iodine (RAI) ablation therapy in differentiated thyroid cancer (DTC). A total of 120 DTC patients who had thyroxine withdrawal either via 4-week hypothyroidism induction (non-treated group, n = 60) or 2-week administration and then 2-week withdrawal of LT3 (LT3-treated group, n = 60) to induce hypothyroid state prior to RAI ablation after initial surgery were included. Complications related to hypothyroidism-induction, Beck Depression Inventory (BDI), Hospital Anxiety-Depression Scale (HADS), and SF-36 health-related quality of life (HRQoL) scores were recorded. In the non-treated group, transition from euthyroid to hypothyroid state was associated with significant increase in the likelihood of moderate-to-severe depression on BDI ($p < 0.001$), presence of depression on HADS-D ($p < 0.001$), presence of anxiety on HADS-A (6.7 % during euthyroid state vs. 33.3 % during hypothyroid state, $p < 0.001$), and major syndrome on BPRS (0.0 vs. 10.0 %, $p = 0.001$) as well as significant decrease in all SF-36 HRQoL domain scores ($p < 0.001$ for each). In conclusion, our findings indicate the likelihood of L3-treatment to enable a more favorable transition period from euthyroid to hypothyroid state without experiencing a deterioration in depression, anxiety, or HRQoL.

Introduction

The intense scrutiny of the thyroid gland and widespread use of ultrasonography and other modern diagnostic techniques have allowed the discovery of a large reservoir of previously undetectable, small, and predominantly papillary thyroid tumors [1, 2]. Hence, the improved population screening within the last decades yielded an over-diagnosis of thyroid cancer, differentiated thyroid cancer (DTC) in particular, incidentally on radiological imaging, as considered to reflect an enhanced detection of subclinical disease rather than an actual increase [2–4]. Accordingly, the health-related quality of life (HRQoL) of thyroid cancer patients has become of great concern to clinicians globally, given the increasing survivor population, a relatively low morbidity of the clinical diagnosis and the likelihood of unnecessary treatment exposures [4–6].

The traditional follow-up of DTC comprises periodic surveillance to detect persistent or recurrent disease with measurement of tumor marker serum thyroglobulin, neck ultrasonography and total body scan with RIA for diagnostic and therapeutic purposes, which necessitates adequately elevated blood levels of thyroid-stimulating hormone (TSH ≥ 30 mU/l) to stimulate sufficient radioactive ^{131}iodine (RAI) uptake [4, 6, 7]. This can be achieved by stopping levothyroxine (LT4) replacement for at least 3 weeks (thyroxine withdrawal) or by intramuscular administration of recombinant human TSH (rhTSH), while alternatively triiodothyronine (LT3) can be administered for 2 weeks followed by LT3-withdrawal for 2 weeks before RAI in an attempt to decrease the duration of hypothyroidism [4, 6, 7].

Thyroxine withdrawal in preparation for RAI induces a profound state of hypothyroidism with associated physical and mental (i. e., depression and anxiety) complaints that may interfere severely with the patient's activities of daily living and may have a profound impact on HRQoL [7, 8].

LT3-treatment strategy prior to RAI ablation therapy with shorter half-life of LT3 is considered a conceptually attractive alternative to shorten the duration of overt hypothyroidism [7, 8]. However, there is limited and controversial data regarding the impact of interim LT3 medication prior to RAI ablation therapy on physical and physiological morbidity among DTC patients as well as the relation of short-term hypothyroid induction with mood disorders (depression and anxiety) and HRQoL [7–10].

This study aimed to compare "non-treated" versus "LT3-treated" protocols of short-term hypothyroidism induction prior to RAI ablation therapy in DTC patients in terms of hypothyroid complications, mood disorders (depression and anxiety), and HRQoL before and after thyroxine withdrawal.

Patients and Methods

Study population

A total of 120 patients with DTC (mean ± SD age: 49.0 ± 10.8 years, 80 % were females) who had thyroxine withdrawal to induce hypothyroid state prior to RAI ablation after initial surgery were included in this prospective study conducted at a tertiary care hospital. ATA risk stratification system was used to estimate the risk of persistent/recurrent disease. Patients were divided into two groups based on characteristics of thyroxine withdrawal period including those followed without treatment during the entire 4-week hypothyroidism induction period (non-treated group, n = 62) (mean ± SD age: 49.7 ± 11.7 years, 81.7 % were females) and those followed with 2-week administration and then 2-week withdrawal of LT3 (LT3-treated group, 25 mcg oral twice daily, n = 58), mean ± SD age: 48.7 ± 9.9 years, 78.3 % were females). Adult patients (over 18 years of age) with operated DTC (papillary thyroid carcinoma) and available data on clinical and laboratory findings related to induction period during their follow up at internal medicine and endocrine clinics were included in the study. Illiteracy, < 18 years or > 65 years of age and presence of comorbid diseases (i. e., malignancy, diabetes mellitus, hepatic failure, kidney failure, hypertension), mental retardation, severe psychotic disorder, organic mental disorder, previous psychiatric illnesses such as depression, anxiety and treatments such as anxiolytics and antidepressants or alcohol and substance abuse were the exclusion criteria.

Written informed consent was obtained from each following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the institutional ethics committee.

Study parameters

Data on patient demographics (age, gender), body mass index (BMI, kg/m^2), complications of hypothyroidism, psychometric instruments including Beck Depression Inventory (BDI), Hospital Anxiety-Depression Scale (HADS) and SF-36 health related quality of life (SF-36 HRQoL) scores, tumor diameter and serum levels for triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone (TSH), thyroglobulin (TG) and anti-thyroglobulin (anti-TG) were recorded in each patient. Patients were evaluated twice during euthyroid state under regular use of thyroxine therapy and during hypothyroid state achieved (with or without LT3 treatment) at the time of RAI ablation planning. Accordingly, patient demographics and hypothyroid complications were evaluated with respect to thyroxine withdrawal method applied for induction of hypothyroid state (non-treated vs. LT3-treated), while psychometrics were evaluated with respect to thyroid status (euthyroid vs. hypothyroid state) and thyroxine withdrawal method applied for induction of hypothyroid state (non-treated vs. LT3-treated). In addition, serum levels for thyroid hormones measured in the euthyroid and hypothyroid state and the tumor diameter were also evaluated with respect to presence vs. absence of depression and/or anxiety based on BDI and HADS categories.

Beck depression inventory (BDI)

BDI is a 21-item self-reporting questionnaire for evaluating the level and change in severity of depression for the past two weeks based on physical, emotional, cognitive and motivational symptoms [11]. Each item is scored on a 4-point scale from 0 (no symptom) to 3 (severe symptoms), while the total score achieved by adding the highest ratings for all 21 items ranges from 0 to 63 with higher scores indicating greater symptom severity [11]. Based on the total score individuals are categorized to have severe depression (scores 30–63), moderate depression (scores 19–29), mild depression (scores 10–18) and minimal level of depression (scores 0–9) [11]. The reliability and validity analysis of Turkish version of BDI was performed by Hisli in 1989 [12].

Hospital anxiety-depression scale (HADS)

The HADS, developed by Zigmond and Snaith [13] is a fourteen item [seven relate to anxiety (HADS-A) and seven relate to depression (HADS-D)] scale used to screen anxiety and depression in medical outpatient settings [13]. Each item on the questionnaire is scored from 0–3 leading overall score to range between 0 and 21 for either anxiety or depression as categorized into normal (scores 0–7), borderline abnormal (scores 8–10) and abnormal (scores 11–21) status [13]. HADS was adapted to Turkish by Aydemir [14].

SF-36 HRQoL

The 36-item Short-form Health Survey (SF-36) is a self-administered questionnaire that measures Health-Related Quality of Life

across eight domains including physical functioning, physical and emotional role limitations, bodily pain, general health perception, vitality, social functioning and mental health [15]. Total scores range from 0 to 100 with higher transformed scores indicating better health status [15].

Statistical analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, version 17.0 (IBM Corp., Armonk, NY, USA). Chi-square (χ^2) test was used for the comparison of categorical data, while numerical data were analyzed using independent sample *t*-test. Change over time was evaluated by the Wilcoxon test. Correlation analysis was performed via Spearman and Pearson tests. Data were expressed as mean ± standard deviation (SD), median (minimum-maximum) and percent (%) where appropriate. p-Value < 0.05 was considered statistically significant.

Results

Patient demographics and complications related to hypothyroidism-induction

Non-treated (mean ± SD age: 49.3 ± 11.7 years, 81.7 % were females) and LT3-treated (mean ± SD age: 48.7 ± 9.9 years, 78.3 % were females) groups were homogenous in terms of patient's demographics. Apart from the hearing loss and slowed movements, all hypothyroid complications were significantly more common in non-treated vs. LT3-treated groups during the hypothyroid state (p ranged 0.032 to < 0.001) (▶ **Table 1**).

▶ **Table 1** Patient demographics and complications related to hypothyroidism-induction.

		Short-term hypothyroidism induction		
		Non-treated (n = 62)	**LT3-treated (n = 58)**	**p-Value**
Patient characteristics				
Age (year), mean ± SD		49.3 ± 11.7	48.7 ± 9.9	0.769[1]
Gender, n (%)				
Female		49 (81.7)	47 (78.3)	0.820[2]
Male		11 (18.3)	13 (21.7)	
BMI (kg/m^2), mean ± SD		28.0 ± 4.5	28.9 ± 4.4	0.227[1]
Hypothyroid complications, n (%)				
Hypohydrosis	Euthyroid state	0 (0.0)	0 (0.0)	–
	Hypothyroid state	8 (13.3)	1 (1.7)	**0.032**
Hoarse voice	Euthyroid state	0 (0.0)	0 (0.0)	–
	Hypothyroid state	31 (51.7)	12 (20.0)	**0.001**
Numbness	Euthyroid state	1 (0.8)	0 (0.0)	–
	Hypothyroid state	35 (58.3)	4 (6.7)	**< 0.001**
Dry skin	Euthyroid state	0 (0.0)	0 (0.0)	–
	Hypothyroid state	54 (90.0)	19 (31.7)	**< 0.001**
Constipation	Euthyroid state	0 (0.0)	0 (0.0)	–
	Hypothyroid state	50 (83.3)	19 (32.2)	**< 0.001**
Weight gain	Euthyroid state	0 (0.0)	0 (0.0)	–
	Hypothyroid state	41 (68.3)	11 (18.3)	**< 0.001**
Hearing loss	Euthyroid state	0 (0.0)	0 (0.0)	–
	Hypothyroid state	6 (10)	1 (1.7)	0.114
Slowed movements	Euthyroid state	0 (0.0)	0 (0.0)	–
	Hypothyroid state	51 (85.0)	41 (68.3)	0.051
Edema	Euthyroid state	0 (0.0)	0 (0.0)	–
	Hypothyroid state	50 (83.3)	14 (23.3)	**< 0.001**
Skin thickening	Euthyroid state	0 (0.0)	0 (0.0)	–
	Hypothyroid state	24 (40.0)	0 (0.0)	**< 0.001**
Cold skin	Euthyroid state	0 (0.0)	0 (0.0)	–
	Hypothyroid state	21 (35.0)	1 (1.7)	**< 0.001**

BMI: Body mass index; LT3: Triiodothyronine.; [1] Independent samples t test, [2] Chi-square test.

Serum levels for thyroid hormones in euthyroid and hypothyroid state in study groups

In the euthyroid state, non-treated versus LT3-treated patients had significantly lower serum levels for T4 [1.4 (0.1–2.8) vs. 1.5 (0–2.4), p = 0.026] and higher levels of anti-TG [1.7 (0.6–74.6) vs. 1.0 (0–108.9), p = 0.001] (▶ **Table 2**).

In the hypothyroid state, non-treated versus LT3-treated patients had significantly higher serum levels for T4 [0.4 (0.4–1) vs. 0.4 (0.4–0.5), p = 0.021], TSH [79 (34.4–100) vs. 56.8 (30.8–100), p = 0.012] and anti-TG [1.4 (0.3–51.1) vs. 0.8 (0.3–97.1), p = 0.005]. No significant difference was noted between non-treated and LT-3 treated patients in terms of serum T3 levels in the euthyroid and hypothyroid state (▶ **Table 2**).

Psychometrics with respect to thyroid status and thyroxine withdrawal method

During the euthyroid state, no significant difference was noted between non-treated and LT3-treated groups in terms of BDI (likelihood of moderate-to-severe depression in 10 % and 5.0 % of patients, respectively), HADS-D (presence of depression in 18.3 % and 15.0 %, respectively) and HADS-A (presence of anxiety in 6.7 % and 13.3 %, respectively) (▶ **Table 3**).

During the hypothyroid state, non-treated vs. LT3-treated group of patients had significantly higher likelihood of moderate-to-severe depression based on BDI (23.3 vs. 8.4 %, p = 0.034) and depression based on HADS-D (45.0 vs. 25.0 %, p = 0.035) (▶ **Table 3**).

SF-36 HRQoL revealed significantly higher role-physical score (p = 0.002), bodily pain score (p = 0.010), vitality score (p = 0.028), social functioning score (p = 0.040) and mental health score (p = 0.044) in the non-treated vs. LT3-treated groups during the euthyroid state, whereas in the hypothyroid state the two groups had similar SF-36 HRQoL scores for each domain (▶ **Table 2**).

In the non-treated group, transition from euthyroid to hypothyroid state was associated with significant increase in the likelihood of moderate-to-severe depression on BDI (from 10.0 % to 23.3 %, p < 0.001), presence of depression on HADS-D (from 18.3 % to 45.0 %, p < 0.001) and presence of anxiety on HADS-A (from 6.7 % to 33.3 %, p < 0.001) as well as significant decrease in all SF-36 HRQoL domain scores (p < 0.001 for each) (▶ **Table 3**).

In the LT3-treated group, no significant change occurred during transition from euthyroid to hypothyroid state in the likelihood of moderate-to-severe depression on BDI (from 5.0 % to 8.4 %, p = 0.428), presence of depression on HADS-D (from 15.0 to 25.0 %, p = 0.056) and presence of anxiety on HADS-A (from 13.3 % to 20.0 %, p = 0.096) as well as in SF-36 HRQoL domain scores (p > 0.05 for each) (▶ **Table 3**).

Serum thyroid hormone levels and the tumor diameter with respect to BDI and HADS scores

In the non-treated group, T3 [3.7 (3–4.1) vs. 3.0 (1.8–4), p < 0.001] and T4 [1.6 (1.3–2.8) vs. 1.4 (1.1–2.4), p = 0.007] levels were significantly higher in those with versus without HADS based depression during euthyroid state, while no significant difference was noted in serum thyroid hormone levels with respect to BDI and HADS-A findings. In the hypothyroid state, serum thyroid hormone levels did not differ significantly with respect to BDI, HADS-D and HADS-A findings (▶ **Table 4**).

▶ **Table 2** Serum levels for thyroid hormones in euthyroid and hypothyroid state in study groups.

		Non-treated (n = 62)	LT-3 treated (n = 58)	p-Value
Thyroid hormone levels		**Median (min-max)**	**Median (min-max)**	
T3	euthyroid	3.1 (1.8–4.1)	3.1 (2–4.5)	0.609
	hypothyroid	1 (1–11)	1 (1–2.5)	0.290
T4	euthyroid	1.4 (0.1–2.8)	1.5 (0–2.4)	**0.026**
	hypothyroid	0.4 (0.4–1.0)	0.4 (0.4–0.5)	**0.021**
TSH	euthyroid	0 (0–2.9)	0 (0–1.3)	0.074
	hypothyroid	79 (34.4–100)	56.8 (30.8–100)	**0.012**
Anti-TG	euthyroid	1.7 (0.6–74.6)	1 (0–108.9)	**0.001**
	hypothyroid	1.4 (0.3–51.1)	0.8 (0.3–97.1)	**0.005**
TG	euthyroid	0.2 (0–0.7)	0.2 (0.2–1.4)	0.599
	hypothyroid	0.2 (0.2–2.4)	0.2 (0.2–0.7)	0.089

T3: Triiodothyronine; T4: Thyroxine; TSH: Thyroid stimulating hormone; TG: Thyroglobulin; anti-TG: Anti-thyroglobulin.

In the L3-treated group, other than significantly higher serum Anti TG levels in patients with vs. without HADS based depression in the euthyroid state, no significant difference was noted in serum thyroid hormone levels with respect to BDI, HADS-D and HADS-A findings in either euthyroid or hypothyroid state (▶ **Table 4**).

SF-36 HRQoL scores with respect to gender, age, tumor diameter in euthyroid and hypothyroid states

Physical functioning, general health and vitality scores were significantly higher in males than in females both in the euthyroid state (p = 0.034, p = 0.003, and p = 0.002, respectively) and hypothyroid state (p < 0.001, p = 0.005, and p = 0.009, respectively). Social functioning (p = 0.008), role-emotional (p < 0.001), and mental health (p = 0.019) scores were also higher in males versus females in the hypothyroid state (▶ **Table 5**).

SF-36 HRQoL scores were not correlated with tumor diameter in euthyroid state, while there was a slightly positive correlation between vitality and tumor diameter (r = 0.184, p = 0.045) in the hypothyroid state (▶ **Table 6**). SF-36 HRQoL scores were not correlated with age in the hypothyroid state, while bodily pain was negatively correlated with age (r = –0.217, p = 0.017) in the euthyroid state (▶ **Table 6**).

Discussion

Our findings revealed considerable disadvantages of using "no treatment strategy" compared to "LT3 treatment strategy" during short-term hypothyroidism induction prior to RAI ablation therapy in patients with DTC. Non-treated patients had higher likelihood of experiencing hypothyroid complications and depression than

▶ **Table 3** Psychometrics with respect to thyroid status and thyroxine withdrawal method applied for induction of hypothyroid state.

	Non-treated (n = 62) (A)			LT3-treated (n = 58) (B)			p-Value (A vs. B)	
	Euthyroid state	Hypothyroid state	p-Value[1]	Euthyroid state	Hypothyroid state	p-Value[1]	Euthyroid	Hypothyroid
BDI category, n(%)								
Minimal level of depression (scores 0–9)	44 (73.3)	30 (50.0)	**<0.001**	46 (76.7)	45 (75.0)	0.428	0.525[2]	**0.034[2]**
Mild depression (scores 10–18)	10 (16.7)	16 (26.7)		11 (18.3)	10 (16.7)			
Moderate depression (scores 19–29)	4 (6.7)	11 (18.3)		3 (5.0)	4 (6.7)			
Severe depression (scores 30–63)	2 (3.3)	3 (5.0)		0 (0.0)	1 (1.7)			
HADS-D, n (%)								
Depression absent (<8)	49 (81.7)	33 (55.0)	**<0.001**	51 (85.0)	45 (75.0)	0.056	0.333[2]	**0.035[2]**
Depression present (>8)	11 (18.3)	27 (45.0)		9 (15.0)	15 (25.0)			
HADS-A, n (%)								
Anxiety absent (<11)	56 (93.3)	40 (66.7)	**<0.001**	52 (96.7)	48 (80.0)	0.096	0.277[2]	0.140[2]
Anxiety present (>11)	4 (6.7)	20 (33.3)		8 (13.3)	12 (20.0)			
SF-36 HRQoL Scores, mean ± SD								
Physical functioning score	86.6 ± 16.1	68.4 ± 23.9	**<0.001**	80.9 ± 18.8	77.4 ± 20.8	0.156	0.076[3]	0.030[3]
Role-physical score	90.2 ± 19.3	66.2 ± 31.2	**<0.001**	73.2 ± 35.8	69.4 ± 39.3	0.457	**0.002[3]**	0.623[3]
Bodily pain score	83.7 ± 18.6	68.0 ± 26.0	**<0.001**	74.1 ± 21.5	68.5 ± 23.7	0.067	**0.010[3]**	0.915[3]
General health score	69.1 ± 17.0	54.9 ± 18.1	**<0.001**	62.9 ± 15.8	59.5 ± 18.1	0.093	0.041[3]	0.17[3]
Vitality score	67.5 ± 17.4	54.9 ± 20.5	**<0.001**	60.8 ± 15.7	59.7 ± 19.0	0.499	**0.028[3]**	0.188[3]
Social functioning score	87.5 ± 18.3	72.9 ± 23.7	**<0.001**	80.2 ± 19.9	74.9 ± 21.2	0.109	**0.040[3]**	0.642[3]
Role-emotional score	79.7 ± 28.1	63.0 ± 32.3	**<0.001**	65.0 ± 31.9	58.1 ± 38.9	0.178	0.009[3]	0.453[3]
Mental health score	71.5 ± 16.5	58.1 ± 17.0	**<0.001**	62.9 ± 15.3	61.6 ± 17.4	0.429	**0.004[3]**	0.255[3]

BDI: Beck Depression Inventory; HADS: Hospital Anxiety-Depression Scale; A: anxiety; D: depression; HRQoL: Health related quality of life; LT3: Triiodothyronine.; [1] Wilcoxon text; [2] Chi-square test; [3] Independent samples t-test.

LT3-treated patients, as well as the marked deterioration in HRQoL and increased risk of experiencing depression, anxiety and major syndrome during transition from euthyroid to hypothyroid state. Also, the interactions between thyroid hormones and depression/anxiety seem to be stronger during the euthyroid rather than hypothyroid state along with stronger adverse impact of hypothyroid state on HRQoL among females.

Similarly, previous studies indicated the association of traditional thyroid hormone withdrawal with hypothyroid symptoms such as fatigue, lethargy, cold intolerance, weight gain and non-pitting edema, as well as with the concomitant psychological morbidity (i. e., depression) which in turn frequently impair the patient QoL [4, 16, 17].

In the current study, all domains of SF-36 HRQoL deteriorated during hypothyroid state in the non-treated group, while no change in SF-36 HRQoL scores from euthyroid to hypothyroid state was apparent in the LT3-treated group. Moreover, non-treated patients were initially had higher SF-36 HRQoL scores (role-physical, bodily pain, vitality, social functioning and mental health) than LT3-treated group during the euthyroid state. Likewise, in a study with 29 DTC patients, QoL was reported to deteriorate after short-term hypothyroidism, especially in physical health and psychological dimensions, along with increase in patient's being feeling depressed and anxious after thyroxine withdrawal [18]. In a cross-sectional study evaluating the SF-36, HADS, BDI and Profile of Mood States (POMS) in 136 DTC patients on thyroid hormone withdrawal for RAI compared to the general population, hypothyroid patients were reported to have significantly impaired HRQoL, higher prevalence of anxiety (62.5 %) but not depression (17.9 %) [19]. The authors concluded that HRQoL is severely impaired in DTC patients under short-term hypothyroidism, with depression and anxiety as the potential predictors of HRQoL impairment [19]. In our study, hypothyroid versus euthyroid state was associated with significant increase in the likelihood of depression and anxiety and deterioration in HRQoL, while deterioration in social functioning, role-emotional

▶ **Table 4** Serum levels for thyroid hormones and the tumor diameter with respect to BDI and HADS scores in euthyroid and hypothyroid state.

		BDI (depression)				HADS-D (depression)			HAD-A (anxiety)		
Median (min–max)		**Minimal (n = 90)**	**Mild (n = 21)**	**Moderate (n = 9)**	**p**	**Absent (n = 100)**	**Present (n = 20)**	**p**	**Absent (n = 108)**	**Present (n = 12)**	**p**
Non-treated (n = 62)											
T3	euthyroid	3.1 (1.8–4.1)	3.1 (2.5–4.1)	3.3 (2.9–4.0)	0.580	3.0 (1.8–4)	3.7 (3–4.1)	**< 0.001**	3.1 (1.8–4.1)	3.3 (2.5–4.1)	0.129
	hypothyroid	1 (1–1.7)	1 (1–11)	1.1 (1–4)	0.297	1 (1–1.6)	1 (1–11)	0.320	1 (1–11)	1 (1–4)	0.781
T4	euthyroid	1.4 (1.1–2.8)	1.4 (0.1–2.1)	1.4 (1.2–2)	0.669	1.4 (1.1–2.4)	1.6 (1.3–2.8)	**0.007**	1.4 (1.1–2.8)	1.6 (1.3–2.1)	0.124
	hypothyroid	0.4 (0.4–0.5)	0.4 (0.4–1)	0.4 (0.4–0.44)	0.795	0.4 (0.4–0.5)	0.4 (0.4–1)	0.667	0.4 (0.4–1)	0.4 (0.4–0.44)	0.851
TSH	euthyroid	0 (0–2.9)	0 (0–0.3)	0 (0–1)	0.835	0 (0–2.9)	0 (0–0.3)	0.078	0 (0–2.9)	0 (0–0.1)	0.882
	hypothyroid	78.4 (37.7–100)	84.3 (34.9–100)	76.7 (34.4–100)	0.815	79.1 (37.7–100)	79 (34.4–100)	0.932	75.2 (34.9–100)	85.6 (34.4–100)	0.612
Anti-TG	euthyroid	1.8 (0.6–74.6)	1 (0.7–5.7)	2.3 (1–35.3)	0.129	1.8 (0.6–74.6)	1.5 (0.6–35.3)	0.226	1.7 (0.6–74.6)	1 (0.8–35.3)	0.590
	hypothyroid	1.2 (0.3–51.1)	1.7 (0.3–11.2)	1.9 (0.4–36.5)	0.374	1.3 (0.3–51.1)	1.7 (0.3–36.5)	0.865	1.2 (0.3–51.1)	1.9 (0.4–36.5)	0.202
TG	euthyroid	0.2 (0–0.7)	0.2 (0–0.3)	0.2 (0.2–0.3)	0.390	0.2 (0–0.7)	0.2 (0–0.6)	0.075	0.2 (0–0.7)	0.2 (0–0.3)	0.294
	hypothyroid	0.2 (0.2–1.7)	0.2 (0.2–0.3)	0.2 (0.2–2.4)	0.812	0.2 (0.2–1.7)	0.2 (0.2–2.4)	0.936	0.2 (0.2–1.7)	0.2 (0.2–2.4)	0.475
Tumor diameter	euthyroid	1.7 (0.5–7)	1.7 (1.1–4.8)	2.3 (1–4.3)	0.943	1.7 (0.5–7)	2.3 (0.8–4.8)	0.592	1.7 (0.7–7)	2 (0.5–4.8)	0.927
	hypothyroid	1.6 (0.7–7)	1.7 (0.5–4.5)	2 (1–4.8)	0.973	1.7 (0.7–7)	1.8 (0.5–4.8)	0.821	1.7 (0.7–7)	1.4 (0.5–4.8)	0.323
LT3-treated (n = 58)											
T3	euthyroid	3.1 (2–4.5)	3 (2.2–4.4)	3.4 (2.9–3.8)	0.814	3 (2–4.2)	3.7 (2.3–4.4)	0.210	3 (2–4.2)	3.6 (2.2–4.5)	0.297
	hypothyroid	1 (1–2.5)	1 (1–1.1)	1 (1–1.3)	0.729	1 (1–2.5)	1 (1–1.3)	0.868	1 (1–2.5)	1 (1–1.5)	0.245
T4	euthyroid	1.5 (1–2.4)	1.6 (0–2.4)	1.5 (1.3–1.6)	0.667	1.5 (0–2.4)	1.6 (1.5–2.1)	0.178	1.5 (1–2.4)	1.8 (0–2.1)	0.166
	hypothyroid	0.4 (0.4–0.4)	0.4 (0.4–0.5)	0.4 (0.4–0.4)	0.299	0.4 (0.4–0.5)	0.4 (0.4–0.4)	0.421	0.4 (0.4–0.5)	0.4 (0.4–0.4)	0.490
TSH	euthyroid	0 (0–1.3)	0 (0–0.7)	0 (0–0.1)	0.125	0 (0–1.3)	0 (0–0.4)	0.926	0 (0–1.3)	0 (0–0.7)	0.426
	hypothyroid	55.9 (30.8–100)	84.9 (38.2–100)	44.5 (37.8–84.8)	0.357	58.6 (30.8–100)	52.7 (37.8–100)	0.813	55.3 (30.8–100)	84.8 (37.8–100)	0.252
Anti-TG	euthyroid	0.9 (0.3–23.1)	1.1 (0–108.9)	0.7 (0.4–1)	0.434	1.2(0–108.9)	0.7 (0.3–1.4)	**0.034**	1 (0–108.9)	0.8 (0.3–2.9)	0.591
	hypothyroid	0.8 (0.3–97.1)	0.8 (0.4–1.8)	0.8 (0.3–4.7)	0.945	0.8(0.3–97.1)	0.7 (0.3–4.7)	0.501	0.8 (0.3–97.1)	0.8 (0.3–4.7)	0.463
TG	euthyroid	0.2 (0.2–0.9)	0.2 (0.2–1.4)	0.2 (0.2–0.2)	0.181	0.2(0.2–1.4)	0.2 (0.2–0.2)	0.374	0.2 (0.2–1.4)	0.2 (0.2–0.7)	0.431
	hypothyroid	0.2 (0.2–0.7)	0.2 (0.2–0.2)	0.2 (0.2–0.2)	0.638	0.2(0.2–0.7)	0.2 (0.2–0.2)	0.320	0.2 (0.2–0.7)	0.2 (0.2–0.2)	0.394
Tumor diameter	euthyroid	1.6 (0.8–8)	2 (0.3–3)	1.3 (1.2–1.8)	0.522	1.7(0.3–8)	1.8 (1–3)	0.539	1.7 (0.8–8)	1.3 (0.3–2.8)	0.287
	hypothyroid	1.7 (0.3–8)	1.8 (1–3.5)	1.8 (1.3–3.6)	0.745	1.7(0.3–8)	1.4 (1–3.6)	0.367	1.7 (0.8–8)	1.4 (0.3–3.6)	0.605

BDI: Beck Depression Inventory; HADS: Hospital Anxiety-Depression Scale; A: anxiety; D: depression; HRQoL: Health related quality of life; T3: Triiodothyronine, T4: Thyroxine; TSH: Thyroid stimulating hormone; TG: Thyroglobulin; anti-TG: Anti-thyroglobulin.

▶ **Table 5** SF-36 HRQoL scores with respect to gender and in euthyroid and hypothyroid states.

	Euthyroid			Hypothyroid		
	Female	**Male**	**p-Value**	**Female**	**Male**	**p-Value**
SF–36 HRQoL scores						
Physical functioning	85 (15–100)	95 (50–100)	**0.034**	70 (5–100)	92.5 (25–100)	**<0.001**
Role-physical	100 (0–100)	100 (25–100)	0.210	75 (0–100)	100 (50–100)	**<0.001**
Bodily pain	74 (22–100)	100 (52–100)	**0.003**	62 (10–100)	92 (0–100)	**<0.001**
General health	66 (15–100)	72 (45–97)	**0.031**	52 (0–100)	72 (30–92)	**0.005**
Vitality	60 (20–100)	75 (55–100)	**0.002**	55 (0–100)	65 (20–100)	**0.009**
Social functioning	100 (37.5–100)	87.5 (37.5–100)	0.899	75 (10–100)	87.5 (38–100)	**0.008**
Role-emotional	66.7 (0–100)	83.4 (1–100))	0.450	66.7 (0–100)	100 (6.7–100)	**<0.001**
Mental health	64 (28–100)	69 (44–92)	0.411	58 (10–100)	66 (52–90)	**0.019**

Data are expressed as median(min–max); HRQoL: Health related quality of life.; Mann–Whitney U-test.

▶ **Table 6** Correlation of SF-36 HRQoL scores with age and tumor diameter in euthyroid and hypothyroid states.

	Euthyroid state		Hypothyroid state	
	Age	**Tumor diameter**	**Age**	**Tumor diameter**
SF-36 HRQoL scores	r, p	r, p	r, p	r, p
Physical functioning	–0.117, 0.120	0.159, 0.084	–0.128, 0.165	0.063, 0.491
Role-physical	–0.075, 0.414	0.002, 0.982	–0.135, 0.141	–0.022, 0.812
Bodily pain	–0.217, **0.017**	0.085, 0.353	–0.130, 0.157	0.099, 0.282
General health	–0.054, 0.555	0.138, 0.132	–0.103, 0.262	0.167, 0.069
Vitality	–0.156, 0.089	–0.020, 0.831	–0.088, 0.338	0.184, **0.045**
Social functioning	–0.088, 0.338	–0.009, 0.918	–0.008, 0.933	0.024, 0.792
Role-emotional	–0.058, 0.528	0.044, 0.630	0.036, 0.695	–0.123, 0.180
Mental health	0.059, 0.523	0.007,0.940	–0.038, 0.681	–0.038, 0.681

HRQoL: Health related quality of life; r: Correlation coefficient.

and mental health specific to hypothyroid state was evident particularly among female patients.

In a study with 18 DTC patients, impaired mental health, general health and social function domains of SF-36 and worsening of affective and physical symptoms were reported during chronic suppressive levothyroxine therapy [20]. The authors concluded that the QoL and psychometric functionality in patients with DTC is not only affected by thyroxine withdrawal but also by long-term treatment with chronic suppressive doses of levothyroxine [20]. Indeed, our findings revealed the association of higher thyroid hormone levels with increased likelihood of depression and anxiety during euthyroid state in the non-treated group.

In the current study, non-treated and LT-3-treated DTC patients had similar rates of possible depression (26.7 % and 23.3 %; moderate-to-severe in 10.0 % and 5.0 %, respectively) and anxiety (6.7 % and 13.3 %, respectively) in the euthyroid period, whereas non-treated DTC patients showed significantly higher rates of possible depression (50.0 % and 25.0 %; moderate-to-severe in 23.3 % and 8.4 %, respectively) and a non-significant trend for increased anxiety (33.3 % and 20.0 %, respectively) in the hypothyroid period. Previous studies revealed that patients with thyroid cancer have different degrees of depression (range 17.9 % to 43.3 %) and anxiety (range, 45.1 % to 62.5 %) [19, 21, 22], while in patients undergoing thyroxine withdrawal, the overall anxiety and depression prevalence was reported to be 63 % and 17 %, respectively [19, 21]. While hypothyroidism is considered to represent an unrecognized risk factor with a marked potential to severely affect mental health, by increasing the age- and gender-adjusted risk for critical mood deterioration by seven-fold [23], patients' psychological flexibility

is also an important factor that negatively correlates with depression and anxiety and dramatically affects patients' QoL [21, 24].

Exact mechanisms underlying the interaction between thyroid function and depression remain unknown [25]. Although patients with thyroid disorders are considered to be more prone to develop depressive symptoms, depression is also suggested to be accompanied by various subtle thyroid abnormalities, including elevated T4 levels, low T3, elevated rT3, a blunted TSH response to TRH or positive anti-thyroid antibodies [25]. Notably, T3 and or T4 levels were significantly higher in our non-treated patients with depression or anxiety in the euthyroid state, whereas during the hypothyroid state, thyroid hormone levels did not differ significantly with respect to BDI, HADS-D and HADS-A in both non-treated and L3-treated groups.

Our findings indicate association of thyroxine withdrawal period with an increased frequency of depression and anxiety along with a significantly reduced HRQoL. In this regard, using LT3 treatment strategy during hypothyroidism induction prior to RAI ablation therapy seems to be a favorable alternative in DTC patients in terms of avoiding the adverse consequences of no treatment strategy (i. e., emergence of hypothyroid complications, depression and anxiety, and deterioration in QoL).

However, some studies also indicated no further impact of LT3 treatment strategy over thyroxine withdrawal in terms of QoL measures [8, 26]. In a study with 291 patients after total thyroidectomy, ablation preparation using withdrawal of LT3 for 2 weeks was reported to be similar to 4 weeks LT4 withdrawal alone, and not to prevent development of profound hypothyroidism [26]. In a prospective study with patients having withdrawal of thyroxine (n = 37) or T3 supplementation (n = 33) the assessment of HRQoL revealed the equivocal benefit of two approaches with no significant benefit of LT3 supplementation over thyroxine withdrawal in terms of HRQoL, except for the emotional domain (QLQ-C30) [8]. Therefore, the authors have suggested developing other alternate strategies to minimize the impact on HRQoL of reduction in the duration of hypothyroidism in thyroxine withdrawal [8].

In addition, on the basis of association of later periods of thyroxine withdrawal with more severe decline in the HR-QoL, and achievement of required TSH levels (≥ 30 mU/l) in majority of DTC patients by the third week, implementation of a shorter (2 or 3 weeks) thyroxine withdrawal is suggested to minimize the impact on HRQoL [27, 28]. Use of rhTSH as opposed to thyroxine withdrawal has also been suggested to an alternate strategy to prevent overt hypothyroidism and to diminish the adverse effects of thyroxine withdrawal in DTC patients, particularly in terms of relatively improved HRQoL [4, 5, 17].

Certain limitations to this study should be considered. First, due to single center design of the present study, generalizing our findings to overall DTC population seems difficult. Second, lack of data on hemodynamic and cardio-metabolic parameters is another limitation, which otherwise would extend the knowledge achieved in the current study.

Conclusion

In conclusion, our findings indicate the association of hypothyroid state induced by thyroxine withdrawal with an increased frequency of hypothyroid complications and increased likelihood of depression and anxiety along with a significantly reduced HRQoL. L3-treatment seems to enable a more favorable transition period from euthyroid to hypothyroid state without experiencing a deterioration in depression anxiety or HRQoL. In addition, the interactions between thyroid hormones and depression/anxiety seem to be stronger in euthyroid state, along with stronger adverse impact of hypothyroid state on HRQoL among females. In this regard, LT3 treatment strategy seems to be a favorable alternate to no-treatment strategy in operated DTC patients (females in particular) prior to RAI ablation therapy in achieving ablation without the detrimental symptoms of overt short-term hypothyroidism induced by thyroxine withdrawal, avoiding the associated risk of mood disorders such as depression and anxiety and the deterioration in HRQoL. Further large scale longitudinal studies are needed to identify the long-term effects of different hypothyroidism induction strategies used before RAI ablation therapy in DTC patients.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Davies L, Welch HG. Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg 2014; 140: 317–322

[2] Welch HG, Black WC. Overdiagnosis in cancer. J Natl Cancer Inst 2010; 102: 605–613

[3] La Vecchia C, Malvezzi M, Bosetti C et al. Thyroid cancer mortality and incidence: a global overview. Int J Cancer 2015; 136: 2187–2195

[4] Duntas LH, Biondi B. Short-term hypothyroidism after levothyroxine-withdrawal in patients with differentiated thyroid cancer: clinical and quality of life consequences. Eur J Endocrinol 2007; 156: 13–19

[5] Walshaw EG, Smith M, Kim D et al. Systematic review of health-related quality of life following thyroid cancer. Tumori 2022; 108: 291–314

[6] Fugazzola L, Elisei R, Fuhrer D et al. 2019 European thyroid association guidelines for the treatment and follow-up of advanced radioiodine-refractory thyroid cancer. Eur Thyroid J 2019: 227–245

[7] Zubeldia JM, Nabi HA, Jiménez del Río M et al. Exploring new applications for Rhodiola rosea: can we improve the quality of life of patients with short-term hypothyroidism induced by hormone withdrawal? J Med Food 2010; 13: 1287–1292

[8] Rajamanickam S, Chaukar D, Siddiq S et al. Quality of life comparison in thyroxine hormone withdrawal versus triiodothyronine supplementation prior to radioiodine ablation in differentiated thyroid carcinoma: a prospective cohort study in the Indian population. Eur Arch Otorhinolaryngol 2022; 279: 2011–2018

[9] Botella-Carretero JI, Gómez-Bueno M, Barrios V et al. Chronic thyrotropin-suppressive therapy with levothyroxine and short-term overt hypothyroidism after thyroxine withdrawal are associated with undesirable cardiovascular effects in patients with differentiated thyroid carcinoma. Endocr Relat Cancer 2004; 11: 345–356

[10] Leboeuf R, Perron P, Carpentier AC et al. L-T3 preparation for whole-body scintigraphy: a randomized-controlled trial. Clin Endocrinol (Oxf) 2007; 67: 839–844

[11] Beck AT, Ward CH, Mendelson M et al. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4: 561–571

[12] Hisli N. Validity and reliability of Beck depression inventory among university students. Psikoloji Dergisi 1989; 7: 3–13 [Turkish].

[13] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67: 361–370

[14] Aydemir O, Guvenir T, Kuey L et al. Reliability and validity of the Turkish version of hospital anxiety and depression scale. Turk Psikiyatri Derg 1997; 8: 280–287

[15] Ware JE, Kosinski M, Bjorner JB et al. User's manual for the SF-36v2 health survey. Lincoln, RI: Quality Metric Incorporated,; 2007

[16] Luster M, Felbinger R, Dietlein M et al. Thyroid hormone withdrawal in patients with differentiated thyroid carcinoma: a one hundred thirty-patient pilot survey on consequences of hypothyroidism and a pharmacoeconomic comparison to recombinant thyrotropin administration. Thyroid 2005; 15: 1147–1155

[17] Schroeder PR, Haugen BR, Pacini F et al. A comparison of short-term changes in health-related quality of life in thyroid carcinoma patients undergoing diagnostic evaluation with recombinant human thyrotropin compared with thyroid hormone withdrawal. J Clin Endocrinol Metab 2006; 91: 878–884

[18] Badihian S, Jalalpour P, Mirdamadi M et al. Quality of life, anxiety and depression in patients with differentiated thyroid cancer under short term hypothyroidism induced by levothyroxine withdrawal. Klin Onkol 2016; 29: 439–444

[19] Tagay S, Herpertz S, Langkafel M et al. Health-related quality of life, depression and anxiety in thyroid cancer patients. Qual Life Res 2006; 15: 695–703

[20] Botella-Carretero JI, Galán JM, Caballero C et al. Quality of life and psychometric functionality in patients with differentiated thyroid carcinoma. Endocr Relat Cancer 2003; 10: 601–610

[21] Lv J, Zhu L, Wu X et al. Study on the correlation between postoperative mental flexibility, negative emotions, and quality of life in patients with thyroid cancer. Gland Surg 2021; 10: 2471–2476

[22] Buchmann L, Ashby S, Cannon RB et al. Psychosocial distress in patients with thyroid cancer. Otolaryngol Head Neck Surg 2015; 152: 644–649

[23] Larisch R, Kley K, Nikolaus S et al. Depression and anxiety in different thyroid function states. Horm Metab Res 2004; 36: 650–653

[24] Hoffmann D, Rask CU, Hedman-Lagerlöf E et al. Efficacy of internet-delivered acceptance and commitment therapy for severe health anxiety: results from a randomized, controlled trial. Psychol Med 2021; 51: 2685–2695

[25] Hage MP, Azar ST. The link between thyroid function and depression. J Thyroid Res 2012; 2012: 590648

[26] Lee J, Yun MJ, Nam KH et al. Quality of life and effectiveness comparisons of thyroxine withdrawal, triiodothyronine withdrawal, and recombinant thyroid-stimulating hormone administration for low-dose radioiodine remnant ablation of differentiated thyroid carcinoma. Thyroid 2010; 20: 173–179

[27] Chow SM, Au KH, Choy TS et al. Health-related quality-of-life study in patients with carcinoma of the thyroid after thyroxine withdrawal for whole body scanning. Laryngoscope 2006; 116: 2060–2066

[28] Piccardo A, Puntoni M, Ferrarazzo G et al. Could short thyroid hormone withdrawal be an effective strategy for radioiodine remnant ablation in differentiated thyroid cancer patients? Eur J Nucl Med Mol Imaging 2018; 45: 1218–1223