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Effect of thyroid-stimulating hormone suppression on quality of life in thyroid lobectomy patients: interim analysis of a multicenter, randomized controlled trial in low- to intermediate-risk thyroid cancer patients (MASTER study)

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Purpose: Current clinical practices favor less or no thyroid-stimulating hormone (TSH) suppression for low- to intermediate-risk thyroid cancer patients who receive thyroid lobectomy. The association of TSH suppression on health-related quality of life (HR-QoL) in patients after thyroid lobectomy is not well studied. This study aimed to evaluate the effect of TSH suppression on patient HR-QoL after thyroid lobectomy.
Methods: This study included patients enrolled in an ongoing, multicenter, randomized controlled study investigating the effects of TSH suppression. Patients were randomized to either the low-TSH group (TSH target range, 0.3–1.99 μIU/mL) or the high-TSH group (TSH target range, 2.0–7.99 μIU/mL). The HR-QoL, hyperthyroidism symptom, and depression

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symptom questionnaires performed preoperatively and 2 weeks and 3 months postoperatively were evaluated.
Results: Total of 669 patients (low-TSH group, 340; high-TSH group, 329) were included. Although total HR-QoL score changes were not different between the 2 groups, the high-TSH group had a significantly higher score in the physical domain at postoperative 3 months (P = 0.046). The 2 groups did not have significant differences in hyperthyroidism and depression scores.
Conclusion: In the short-term postoperative period, the physical HR-QoL scores in thyroid lobectomy patients were better when they did not receive TSH suppression. This study suggests the importance of considering HR-QoL when setting TSH suppression targets in thyroid lobectomy patients.
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Key Words: Thyroid neoplasms, Health-related quality of life, Thyroidectomy, Thyrotropin

INTRODUCTION

Recent clinical practices favor less aggressive treatments for patients with low-risk thyroid cancer, considering low disease-specific mortality and younger age at diagnosis [1,2]. More conservative approaches such as thyroid lobectomy (TL), thermal ablation, and active surveillance are increasingly used as alternative treatments to conventional total thyroidectomy in these patients [3]. In addition, postoperative treatments have been moderated in low-risk thyroid cancer; radioactive iodine remnant ablation is no longer recommended, and the benefit of strong thyroid-stimulating hormone (TSH) suppression is increasingly questioned [1,2].

Indeed, conventional TSH suppression to <0.1 mIU/L is no longer performed in low- to intermediate-risk thyroid cancer patients and the 2015 American Thyroid Association guideline recommends maintaining TSH level in the mid to lower normal range (0.5–2 mU/L) in TL patients [1,4]. The oncologic benefits of TSH suppression to <2 mU/L in TL patients, however, are controversial. Jonklaas et al. [5] showed no survival benefit of TSH suppression in stage I thyroid cancer patients nor in stage II patients with TSH levels <2.0 mIU/L. In contrast, Carhill et al. [6] showed that modest TSH suppression of subnormal to normal range improved oncologic survival in low- to high-risk thyroid cancers. However, these studies used heterogeneous populations, including both TL and total thyroidectomy patients. Few retrospective studies have focused on TL patients to study the effect of TSH suppression; however, they showed no survival benefits of TSH suppression to <2 mU/L in these patients [4,7]. Due to insufficient evidence, the 2015 American Thyroid Association guideline only weakly recommends a TSH suppression level to 0.5–2 mU/L in TL patients, and some clinicians even omit TSH suppression due to its weak evidence [1]. Therefore, more prospective studies are warranted to find optimal postoperative TSH levels for positive outcomes in TL patients.

Since differentiated thyroid cancer patients have good long-term survival, management beyond improving the oncologic outcome is essential, and considering health-related quality of life (HR-QoL) is key to improving treatment quality. HR-QoL can be reduced by TSH suppression therapy due to its cardiovascular, musculoskeletal, and cognitive side effects, which can occur when TSH levels are severely suppressed [8,9]. Studies investigating the association between TSH suppression levels and HR-QoL have conflicting results. Yaniv et al. [10] showed that patients who received TSH suppression therapy that lowered TSH levels to <0.5 μIU/mL had worse self-assessment QoL scores than those who did not have suppression therapy. By contrast, in a study that compared HR-QoL among 3 different TSH suppression levels, Monzani et al. [11] showed lower QoL in the TSH replacement group (TSH, normal range) than in the complete suppression group (TSH, <0.01 μIU/mL). However, these studies neither specifically focused on patients who received TL, nor reflected recent practices of a mild or omission of TSH suppression. Therefore, studies focusing on HR-QoL among patients with varied TSH levels from normal to high ranges are necessary to reflect real clinical settings.

This study evaluated postoperative HR-QoL changes in TL patients with low- to intermediate-risk thyroid cancer who received TSH suppression to within the recommended range (<2 mIU/L) or higher (≥2 mIU/L). As part of the Multicenter, Randomized Controlled study for Assessing the Usefulness of Suppressing Thyroid Stimulating Hormone Target Levels after Thyroid Lobectomy in Low to Intermediate Risk Thyroid Cancer Patients (MASTER) study, HR-QoL changes were evaluated up to 3 months postoperatively as an interim analysis.

METHODS

Ethics statement

This study was approved by each Institutional Review Board of the participating hospitals, including the Institutional Review Board of Seoul National University Bundang Hospital

(No. B-2006-618-403). Informed consent was taken from all patients enrolled from the 9 referral hospitals included in our study. The protocol of the study was registered at the Clinical Research Information Service of the Korea Centers for Disease Control and Prevention (No. KCT0004989).

Patient selection and randomization

Patients were selected from the cohort of the MASTER study, the protocol of which was detailed previously [12]. Inclusion criteria were as follows: (1) male or nonpregnant female aged between 19 and 79 years old, (2) biopsy-proven papillary thyroid cancer (PTC) requiring TL, (3) no gross extrathyroidal extension to adjacent structures (nerve, vessel, trachea, etc.) with a tumor size of ≤4 cm and clinical N0 or N1a stage, (4) no or benign nodules in the contralateral thyroid lobe, and (5) agreement to performing questionnaires. Exclusion criteria were as follows: (1) pT4, pN1b, or M1 stage cancer, (2) aggressive histological variant (poorly differentiated, anaplastic, or diffuse sclerosing types) or histological types other than PTC, (3) necessity for completion thyroidectomy, (4) incomplete tumor resection, (5) nodules in the contralateral thyroid lobe diagnosed as follicular neoplasm or malignancy on fine needle aspiration, (6) active hyperthyroidism, and (7) concurrent operation of another organ.

Subjects were randomized into the low-TSH (target range, 0.3–1.99 μIU/mL) or the high-TSH (target range, 2.00–7.99 μIU/mL) group after surgery. Levothyroxine (LT4) was either withheld or prescribed at minimal dosages after surgery, adjusted according to the patient's preexisting thyroid hormone levels regardless of the randomization group (Supplementary Table 1). Patient follow-up visits were at 2 weeks, 3 months, 6 months, 12 months, 18 months, and 24 months postoperatively and then at 1-year intervals until 5 years postoperatively. The randomization was finalized prior to the postoperative 2-week follow-up visit, at which point the dosage adjustment began. Patients received thyroid function tests as part of a routine clinical assessment at every visit, and LT4 dosages were adjusted when the TSH levels were out of target ranges, according to our previously determined adjustment protocol [12].

From May 2020 to February 2022, a total of 680 patients from the MASTER cohort were included in our study. Two patients who received completion thyroidectomy and 9 patients who underwent concurrent operation of another organ were excluded. A total of 669 patients (low-TSH group, 340; high-TSH group, 329) were included in the analysis. A flowchart detailing patient selection and questionnaire response is shown in Fig. 1.

Questionnaires

Patients were asked to perform questionnaires preoperatively and at each postoperative follow-up. Surveys answered at preoperative (Pre), postoperative 2 weeks ± 14 days (PO2W), and postoperative 3 months ± 45 days (PO3M) were evaluated. The Korean version of the self-reported thyroid-specific QoL questionnaire for thyroid cancer patients (KT-QoL) was used to assess HR-QoL, which was initially created by Dow et al. [13] and validated by Ryu et al. [14]. This questionnaire specifically evaluates the domains of physical, psychological, social, and spiritual HR-QoL in thyroid cancer patients. Questions related to radioactive iodine therapy, whole-body scans, and radiation therapy were excluded from the analysis. Responses were scored between 0 (worst outcome) and 10 (best outcome). The mean scores of answered questions were analyzed separately

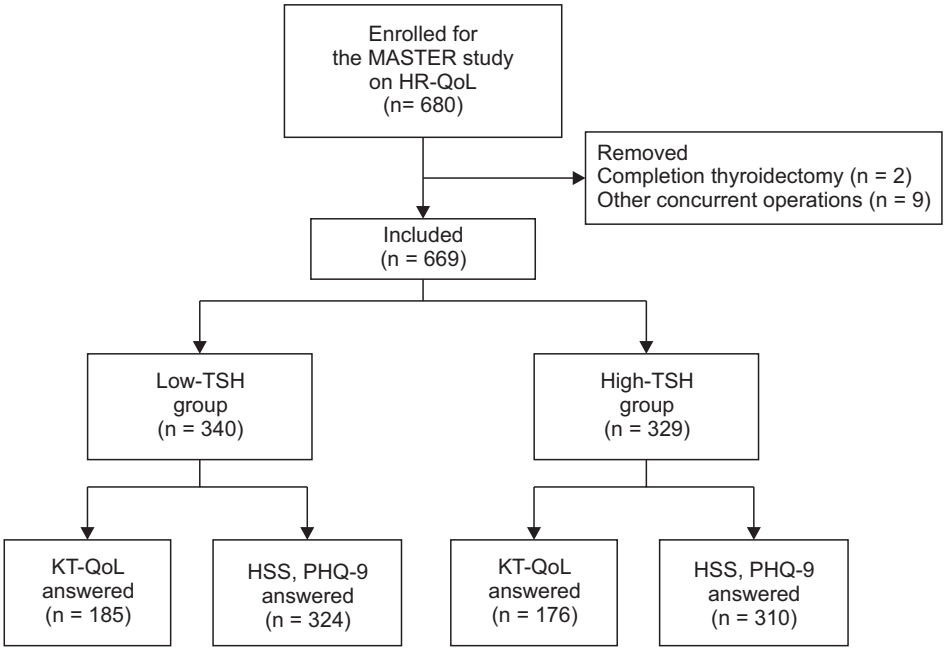

Fig. 1. Flow chart of the study population. MASTER, Multicenter, Randomized Controlled study for Assessing the Usefulness of Suppressing Thyroid Stimulating Hormone Target Levels after Thyroid Lobectomy in Low to Intermediate Risk Thyroid Cancer Patients; HR-QoL, health-related quality of life; TSH, thyroid-stimulating hormone; KT-QoL, Korean version of the self-reported thyroid-specific quality-of-life questionnaire; HSS, hyperthyroidism symptom scale questionnaire; PHQ-9, Patient Health Questionnaire-9 (depression scores).

for each domain of HR-QoL. Additionally, surveys to evaluate hyperthyroidism and depression were performed as these symptoms may affect patient HR-QoL. The Korean version of the hyperthyroidism symptom scale (HSS) originally developed by Klein et al. [15] and validated by Lee et al. [16] was used to evaluate hyperthyroidism symptoms. The Korean version of the Patient Health Questionnaire-9 (PHQ-9) survey created by Kroenke et al. [17] and validated by Park et al. [18] was used for depression analysis. Both questionnaires use higher scores to indicate greater symptoms of hyperthyroidism or depression.

Statistical analyses

Continuous variables are shown as means ± standard deviations. Categorical variables are shown as numbers (percentages). The Student t-tests and chi-square tests were used to compare continuous and categorical variables, respectively. To evaluate repeated measurements of KT-QoL scores, linear mixed model analyses were performed using subject-specific random effects. The model was adjusted for age, sex, smoking status, and comorbidity status. Considering the association of free thyroxine (fT4) levels with TSH levels, an interaction term of the TSH group, PO3M fT4, and time (Pre, PO2W, PO3M) was included as a fixed effect in the linear mixed model. The same model was used for HSS and PHQ-9 analyses. The results from linear mixed model analyses are presented as estimate coefficient (β), 95% confidence interval, and P-value for each fixed effect variable. Spearman correlation analysis was used to find associations between thyroid hormone levels at each time point. Statistical analysis was performed using R software (ver. 4.2.1, R Foundation for Statistical Computing). A P-value less than 0.5 was considered statistically significant.

RESULTS

Clinical and operative information

Patients were enrolled from 9 institutions participating in the MASTER study. Among the 669 patients who met the inclusion criteria, 361 patients (54.0%) and 634 patients (94.8%) responded to KT-QoL and HSS/PHQ-9 questionnaires, respectively (Fig. 1, Table 1). Patient and tumor characteristics in the low- and high-TSH groups were comparable, except for smoking status, as there were significantly fewer current smokers in the high-TSH group (P = 0.048) (Table 2). Characteristics from the subset of patients who responded to the KT-QoL questionnaire were consistent with the whole group. The surgical approach and outcomes were not significantly different between the low- and high-TSH groups (Table 3), with few patients (n = 15, 2.2%) experiencing minor complications such as transient vocal cord palsy or postoperative seroma. Surgical outcomes from the subset of patients who responded to the KT-QoL questionnaire were consistent with the whole group, as well (Table 3).

Levothyroxine dosages and thyroid hormone levels

The numbers of patients who received LT4 treatment at each follow-up visit were not different between the 2 groups. However, the prescribed LT4 dosages were significantly higher in the low-TSH group at PO2W (Supplementary Table 1). In all enrolled patients, the PO3M fT4 level was significantly higher in the low-TSH group than in the high-TSH group (P = 0.022) (Table 4). Thyroid hormone differences were consistent with all enrolled patients in the subset of patients who completed the KT-QoL questionnaire (Table 4). In patients who answered KT-QoL, PO3M TSH levels were lower in the low-TSH group, although the difference was not statistically significant (2.75 ± 2.63 μIU/mL *vs.* 3.98 ± 7.96 ng/dL, P = 0.102). The levels of TSH, fT4, and triiodothyronine (T3) showed significant correlations with themselves across different time points (Pre, PO2W, and PO3M) (Supplementary Fig. 1).

Parameters associated with KT-QoL scores

The observed KT-QoL values at Pre, PO2W, and PO3M time points are shown in Fig. 2. Baseline scores were comparable

Table 1. Frequency of responses to each survey

Variable	No. of patients	Total responded[a]	Preoperative	PO2W	PO3M
Total	669	361 (54.0)	281 (42.0)	310 (46.3)	290 (43.3)
KT-QoL					
Low-TSH group	340	185 (54.4)	140 (41.2)	159 (46.8)	145 (42.6)
High-TSH group	329	176 (53.5)	141 (42.9)	151 (45.9)	145 (44.1)
HSS, PHQ-9					
Low-TSH group	340	324 (95.3)	153 (45.0)	279 (82.1)	255 (75.0)
High-TSH group	329	310 (94.2)	157 (47.7)	274 (83.3)	256 (77.8)

Values are shown as number only or number (percentage). Missing data values were excluded.
PO2W, postoperative 2 weeks; PO3M postoperative 3 months; KT-QoL, Korean version of the self-reported thyroid-specific quality of life questionnaire for thyroid cancer patients; TSH, thyroid-stimulating hormone; HSS, hyperthyroidism symptom scale; PHQ-9, Patient Health Questionnaire-9 (depression scores).
[a]Patients answered any of the preoperative, PO2W, and PO3M surveys.

Table 2. Baseline characteristics of the study population

Characteristic	All enrolled patients			Patients responded to KT-QoL		
	Low-TSH	High-TSH	P-value	Low-TSH	High-TSH	P-value
No. of patients	340	329		185	176	
Age (yr)	46.23 ± 11.69	45.70 ± 11.52	0.557	45.12 ± 11.67	45.38 ± 11.52	0.830
Sex			>0.999			0.750
Male	86 (25.3)	83 (25.2)		50 (27.0)	44 (25.0)	
Female	254 (74.7)	246 (74.8)		135 (73.0)	132 (75.0)	
BMI (kg/m^2)	25.14 ± 4.12	24.77 ± 4.13	0.242	25.33 ± 4.32	24.77 ± 4.33	0.220
Menopausal status[a]			0.544			0.975
Yes	93 (36.8)	77 (31.2)		41 (30.6)	38 (28.6)	
Hysterectomy state	16 (6.3)	15 (6.1)		10 (7.5)	9 (6.8)	
No	143 (56.5)	153 (61.9)		82 (61.2)	85 (63.9)	
Smoking			0.048*			0.048*
Never	280 (82.6)	276 (83.9)		151 (82.1)	141 (80.1)	
Previous	29 (8.6)	38 (11.6)		14 (7.6)	25 (14.2)	
Current	30 (8.8)	15 (4.6)		19 (10.3)	10 (5.7)	
Drinking			0.730			0.958
Never	182 (53.7)	184 (55.9)		93 (50.5)	91 (51.7)	
Previous	32 (9.4)	26 (7.9)		6 (3.3)	5 (2.8)	
Current	125 (36.9)	119 (36.2)		85 (46.2)	80 (45.5)	
Tumor subtype			0.828			0.999
Conventional	261 (77.0)	258 (78.7)		168 (91.3)	160 (91.4)	
Follicular	2 (0.6)	3 (0.9)		2 (1.1)	2 (1.1)	
Solid	62 (18.3)	55 (16.8)		3 (1.6)	3 (1.7)	
Oxyphilic	1 (0.3)	0 (0)		0 (0)	0 (0)	
Others	13 (3.8)	12 (3.7)		11 (6.0)	10 (5.7)	
Tumor number	1.28 ± 0.54	1.26 ± 0.59	0.632	1.29 ± 0.52	1.30 ± 0.64	0.882
Tumor size (cm)	0.84 ± 0.48	0.87 ± 0.48	0.327	0.84 ± 0.45	0.90 ± 0.44	0.241
Stage			0.846			0.248
I	318 (93.5)	304 (92.4)		173 (93.5)	156 (88.6)	
II	21 (6.2)	24 (7.3)		11 (5.9)	19 (10.8)	
Comorbidity			0.357			>0.999
No	198 (58.4)	204 (62.2)		118 (64.1)	113 (64.6)	
Yes	141 (41.6)	124 (37.8)		66 (35.9)	62 (35.4)	
Comorbidity type[b]			0.054			0.042*
Diabetes	27 (19.4)	10 (8.1)		15 (23.1)	6 (9.7)	
Hypertension	49 (35.3)	54 (43.5)		24 (36.9)	31 (50.0)	
Dyslipidemia	17 (12.2)	20 (16.1)		6 (9.2)	8 (12.9)	
Cardiovascular/neurological disease	4 (2.9)	2 (1.6)		3 (4.6)	1 (1.6)	
Osteoporosis	5 (3.6)	5 (4.0)		1 (1.5)	3 (4.8)	
Asthma/COPD	0 (0)	1 (0.8)		0 (0.0)	0 (0)	
Estrogen therapy	6 (4.3)	0 (0.0)		3 (4.6)	0 (0)	
Rheumatoid arthritis	1 (0.7)	1 (0.8)		0 (0)	1 (1.6)	
Fracture history	0 (0)	1 (0.8)		0 (0)	1 (1.6)	
Other cancer history	7 (5.0)	3 (2.4)		5 (7.7)	0 (0)	
Others	23 (16.5)	27 (21.8)		8 (12.3)	11 (17.7)	
Family history of thyroid disease			0.278			0.531
No	302 (89.1)	283 (86.0)		161 (87.5)	149 (84.7)	
Yes	37 (10.9)	46 (14.0)		23 (12.5)	27 (15.3)	

Values are shown as number only, number (%), or mean ± standard deviation. Missing data values were excluded.
KT-QoL, Korean version of the self-reported thyroid-specific quality of life questionnaire for thyroid cancer patients; TSH, thyroid-stimulating hormone; BMI, body mass index; COPD, chronic obstructive pulmonary disease.
[a]In female only. [b]In patients with comorbidity only.
*P < 0.05.

Table 3. Operative approach and outcomes

Variable	All enrolled patients			Patients responded to KT-QoL		
	Low-TSH (n = 340)	High-TSH (n = 329)	P-value	Low-TSH (n = 185)	High-TSH (n = 176)	P-value
Operation approach			0.204			>0.999
Open	263 (77.6)	250 (76.0)		128 (69.6)	122 (69.3)	
Endoscopic	0 (0)	3 (0.9)		0 (0)	0 (0)	
Robotic	76 (22.4)	76 (23.1)		56 (30.4)	54 (30.7)	
Operation time (min)	89.9 ± 36.2	90.5 ± 33.2	0.830	82.9 ± 36.6	80.4 ± 30.3	0.517
Hospital stay (day)	2.5 ± 1.0	2.6 ± 1.0	0.651	2.4 ± 0.8	2.3 ± 0.7	0.652
Vocal cord palsy			>0.999			>0.999
Transient	7 (2.1)	7 (2.1)		7 (3.8)	7 (4.0)	
Permanent	0 (0)	0 (0)		0 (0)	0 (0)	
Seroma	0 (0)	1 (0.3)	0.983	0 (0)	0 (0)	NA

Values are shown as number (%) or mean ± standard deviation. Missing data values were excluded.
KT-QoL, Korean version of the self-reported thyroid-specific quality of life questionnaire for thyroid cancer patients; TSH, thyroid-stimulating hormone; NA, not available.

Table 4. Thyroid hormone levels at each time point

Timepoint	Thyroid hormone level	All enrolled patients				Patients responded to KT-QoL			
		Total (n = 669)	Low-TSH (n = 340)	High-TSH (n = 329)	P-value	Total (n = 361)	Low-TSH (n = 185)	High-TSH (n = 176)	P-value
Pre-operative	TSH (μIU/mL)	1.99 ± 1.48	2.00 ± 1.75	1.98 ± 1.14	0.844	1.90 ± 1.12	1.90 ± 1.1	1.89 ± 1.14	0.981
	fT4 (ng/dL)	1.22 ± 0.16	1.23 ± 0.16	1.21 ± 0.16	0.349	1.24 ± 0.16	1.24 ± 0.16	1.24 ± 0.16	0.805
	T3 (ng/dL)	121.59 ± 23.06	122.09 ± 22.66	121.07 ± 23.51	0.617	116.5 ± 23.44	116.7 ± 21.9	116.2 ± 25.04	0.851
PO2W	TSH (μIU/mL)	3.21 ± 3.47	3.30 ± 4.12	3.13 ± 2.59	0.561	3.31 ± 3.69	3.58 ± 4.68	3.02 ± 2.14	0.206
	fT4 (ng/dL)	1.21 ± 0.26	1.21 ± 0.20	1.21 ± 0.31	0.871	1.21 ± 0.24	1.22 ± 0.24	1.21 ± 0.24	0.802
	T3 (ng/dL)	127.13 ± 25.73	127.28 ± 26.84	126.97 ± 24.63	0.918	124.3 ± 28.26	120.6 ± 23.33	128.61 ± 33.02	0.296
PO3M	TSH (μIU/mL)	3.15 ± 4.57	2.90 ± 2.96	3.41 ± 5.78	0.221	3.35 ± 5.89	2.75 ± 2.63	3.98 ± 7.96	0.102
	fT4 (ng/dL)	1.18 ± 0.17	1.20 ± 0.19	1.17 ± 0.15	0.022*	1.18 ± 0.19	1.21 ± 0.22	1.15 ± 0.16	0.015*
	T3 (ng/dL)	119.64 ± 23.80	119.15 ± 24.22	120.13 ± 23.42	0.696	107.4 ± 22.12	107.2 ± 21.27	107.60 ± 23.07	0.902

Values are shown as mean ± standard deviation.
KT-QoL, Korean version of the self-reported thyroid-specific quality of life questionnaire for thyroid cancer patients; TSH, thyroid-stimulating hormone; fT4, free thyroxine; T3, triiodothyronine; PO2W, postoperative 2 weeks; PO3M, postoperative 3 months.
Normal ranges of thyroid hormones: TSH, 0.3–4.0 μIU/mL; fT4, 0.93–1.70 ng/dL; T3, 81–197 ng/dL.
*$P < 0.05$.

between the 2 TSH groups. Results from the linear mixed model analyses on KT-QoL scores are shown in Table 5. Older age was associated with higher HR-QoL scores among all parameters except the physical domain. Male sex was associated with higher scores in all but spiritual domains. Current smoking status was significantly associated with lower physical HR-QoL scores ($\beta = -0.67$, $P = 0.013$). Total scores were not significantly altered postoperatively compared with baseline HR-QoL scores (PO2W and PO3M *vs.* Pre, both $P > 0.05$). Among the 4 QoL domains (physical, psychological, social, and spiritual), the score for physical HR-QoL was significantly higher in the high-TSH group at PO3M compared to the low-TSH group ($\beta = 2.51$, $P = 0.046$). The score for psychological HR-QoL significantly improved after surgery in all patients (PO2W and PO3M *vs.* Pre, both $P < 0.05$).

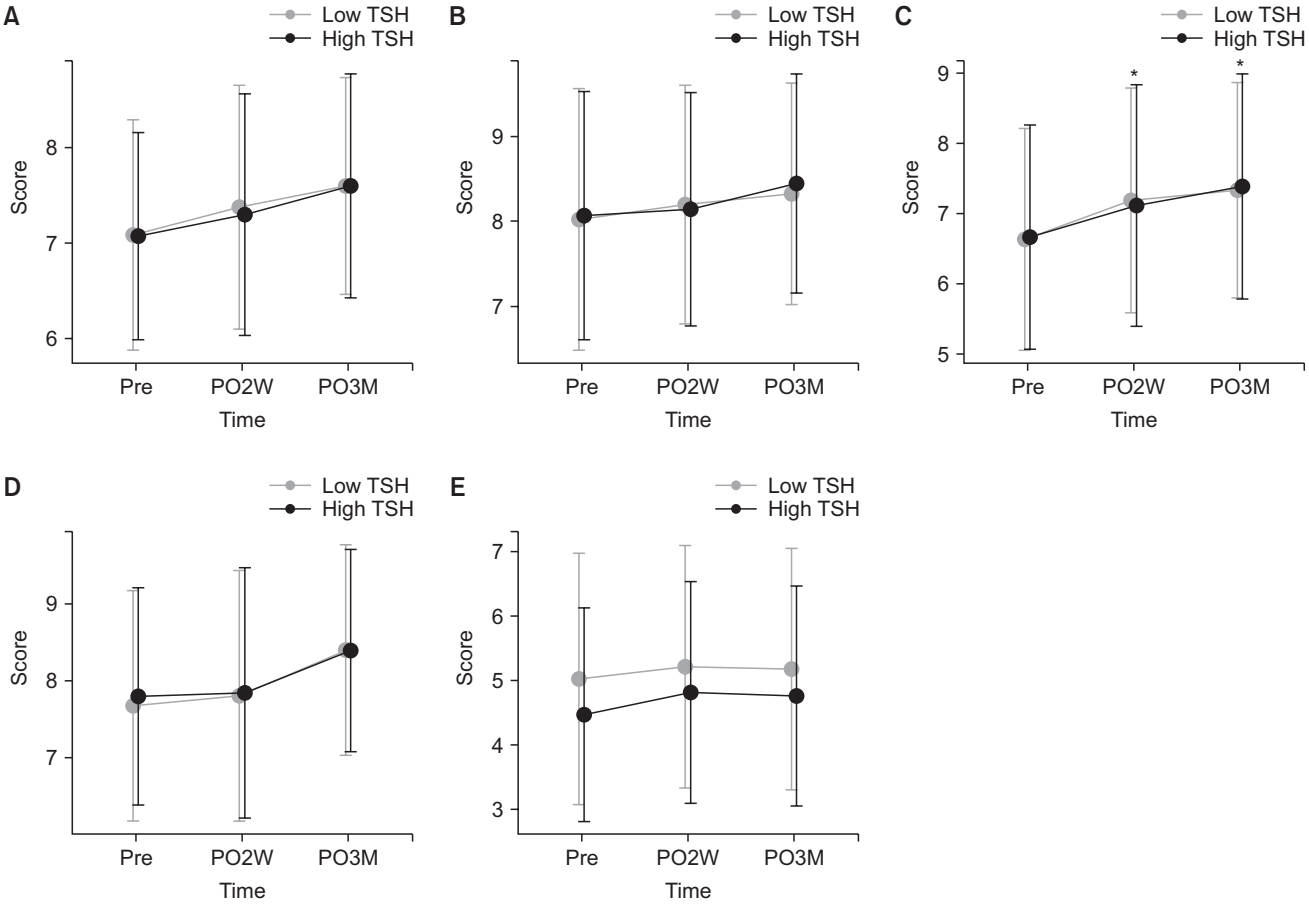

Fig. 2. Observed values of health-related quality of life by thyroid-stimulating hormone (TSH) groups. Mean scores from the Korean version of the self-reported thyroid-specific quality-of-life questionnaire in each follow-up. (A) Total scores. (B) Physical domain. (C) Psychological domain. (D) Social domain. (E) Spiritual domain. Pre, preoperative; PO2W, postoperative 2 weeks; PO3M, postoperative 3 months.
*Significant increase compared to preoperative scores in all patients ($P < 0.05$).

Parameters associated with HSS and PHQ-9 scores

Observed mean scores from the HSS and PHQ-9 questionnaires are shown in Fig. 3. The linear mixed model analyses for HSS and PHQ-9 scores showed no significant associations between the TSH group and postoperative score changes (Table 6). Males had significantly lower HSS ($P = 0.014$) and PHQ-9 scores ($P = 0.002$) than females. Current smokers had significantly greater HSS ($P = 0.009$) and PHQ-9 scores than nonsmokers ($P = 0.003$). Patients with comorbidities had significantly higher HSS ($P = 0.013$) and PHQ-9 ($P = 0.006$) scores than those without comorbidities.

DISCUSSION

In the present study, we found that maintaining TSH at low (low-TSH; 0.3–1.99 μIU/mL) or high (high-TSH; 2.00–7.99 μIU/mL) levels did not affect total HR-QoL changes in the short-term; however, in the physical domain, the high-TSH group had better scores than the low-TSH group after 3 months of surgery. Surprisingly, patients generally did not experience a decrease in HR-QoL after TL, and the psychological scores even improved. In line with previous studies, greater age and male sex were associated with better HR-QoL scores [11,19]. Current smokers had worse physical HR-QoL scores and greater hyperthyroidism and depression symptoms.

TL patients experience better postoperative HR-QoL than total thyroidectomy patients, and this difference is at its highest after 3 months of surgery [20]. This is probably because TL patients are unlikely to experience major complications and are less likely to take LT4 treatment. Nevertheless, mild deterioration of HR-QoL still occurs in TL patients, which subsequently recover after 1–2 years [13,20,21]. While most maintain adequate thyroid function, TL patients have a variety of thyroid hormone levels, with 26% requiring lifelong LT4 treatment [22]. Each patient's remaining thyroid function can also fluctuate at different postoperative time points; Bae et al. [23] showed that TSH levels were at their highest at 3–6 months after TL, as the percentage of patients with TSH level >2 mIU/

Table 5. Fixed effects table for the linear mixed-effects model of KT-QoL scores

Variable	Total			Physical			Psychological			Social			Spiritual		
	Estimates	95% CI	P-value	Estimates	95% CI	P-value	Estimates	95% CI	P-value	Estimates	95% CI	P-value	Estimates	95% CI	P-value
(Intercept)	7.17	5.76 to 8.58	<0.001*	9.35	7.72 to 10.98	<0.001*	6.06	4.10 to 8.01	<0.001*	8.02	6.28 to 9.77	<0.001*	3.62	1.30 to 5.93	0.002*
Age	0.02	0.01 to 0.03	0.001*	–0.01	–0.00 to 0.02	0.119	0.02	0.00 to 0.04	0.014*	0.02	0.01 to 0.04	0.003*	0.03	0.01 to 0.05	0.002*
Male sex (*vs.* female)	0.62	0.29 to 0.95	<0.001*	0.84	0.48 to 1.20	<0.001*	0.89	0.43 to 1.34	<0.001*	0.46	0.07 to 0.85	0.020*	–0.18	–0.73 to 0.38	0.534
Smoking															
Past smoker (*vs.* nonsmoker)	0.02	–0.45 to 0.50	0.920	–0.24	–0.77 to 0.29	0.373	0.31	–0.35 to 0.97	0.360	–0.03	–0.60 to 0.55	0.924	–0.12	–0.95 to 0.70	0.768
Current smoker (*vs.* nonsmoker)	–0.38	–0.86 to 0.10	0.124	–0.67	–1.20 to –0.14	0.013*	–0.09	–0.76 to 0.58	0.797	–0.35	–0.91 to 0.21	0.218	–0.56	–1.37 to 0.26	0.181
Comorbidity (*vs.* none)	–0.15	–0.43 to 0.12	0.269	–0.02	–0.32 to 0.28	0.897	–0.24	–0.62 to 0.14	0.220	–0.07	–0.39 to 0.25	0.668	–0.24	–0.70 to 0.23	0.316
Treatment group, high-TSH (*vs.* low-TSH)	–0.79	–2.78 to 1.19	0.432	–2.16	–4.49 to 0.17	0.070	0.14	–2.61 to 2.89	0.921	–0.16	–2.67 to 2.34	0.899	–1.31	–4.54 to 1.92	0.427
PO3M fT4	–0.70	–1.68 to 0.27	0.158	–1.52	–2.67 to –0.37	0.010*	–0.24	–1.60 to 1.12	0.731	–0.90	–2.13 to 0.33	0.151	0.25	–1.35 to 1.84	0.762
Time															
PO2W (*vs.* Pre)	1.03	–0.12 to 2.19	0.080	–0.09	–1.64 to 1.45	0.906	1.85	0.26 to 3.45	0.023*	1.66	–0.02 to 3.34	0.053	0.46	–1.24 to 2.16	0.593
PO3M (*vs.* Pre)	0.61	–0.52 to 1.74	0.286	–0.92	–2.43 to 0.58	0.229	1.72	0.15 to 3.28	0.031*	1.24	–0.40 to 2.87	0.139	–0.16	–1.82 to 1.51	0.855
Interaction terms															
High-TSH × PO3M fT4	0.58	–1.09 to 2.26	0.494	1.89	–0.08 to 3.85	0.060	–0.16	–2.48 to 2.17	0.894	0.04	–2.07 to 2.16	0.968	0.57	–2.16 to 3.31	0.681
High-TSH × PO2W	0.29	–1.58 to 2.16	0.761	1.15	–1.35 to 3.65	0.366	–0.13	–2.73 to 2.46	0.919	–0.74	–3.46 to 1.99	0.594	1.52	–1.24 to 4.28	0.281
High-TSH × PO3M	1.22	–0.63 to 3.07	0.196	2.51	0.05 to 4.97	0.046*	1.72	–0.84 to 4.28	0.187	–0.72	–3.40 to 1.96	0.598	0.77	–1.96 to 3.49	0.580
PO3M fT4 × PO2W	–0.67	–1.58 to 0.25	0.152	0.22	–1.00 to 1.44	0.723	–1.11	–2.37 to 0.16	0.086	–1.35	–2.69 to –0.02	0.046*	–0.26	–1.61 to 1.08	0.699
PO3M fT4 × PO3M	–0.16	–1.06 to 0.73	0.719	1.01	–0.18 to 2.21	0.097	–0.91	–2.16 to 0.33	0.148	–0.55	–1.86 to 0.75	0.405	0.11	–1.21 to 1.43	0.870
High-TSH × PO3M fT4 × PO2W	–0.31	–1.88 to 1.25	0.694	–1.05	–3.14 to 1.04	0.325	–0.05	–2.22 to 2.12	0.964	0.61	–1.67 to 2.89	0.599	–1.22	–3.53 to 1.08	0.298
High-TSH × PO3M fT4 × PO3M	–1.02	–2.57 to 0.53	0.198	–2.09	–4.16 to –0.02	0.047*	–1.51	–3.66 to 0.64	0.167	0.62	–1.63 to 2.87	0.590	–0.44	–2.73 to 1.84	0.702

KT-QoL, Korean version of the self-reported thyroid-specific quality of life questionnaire for thyroid cancer patients; CI, confidence interval; TSH, thyroid-stimulating hormone; PO3M, postoperative 3 months; fT4, free thyroxine; PO2W, postoperative 2 weeks.
*P < 0.05.

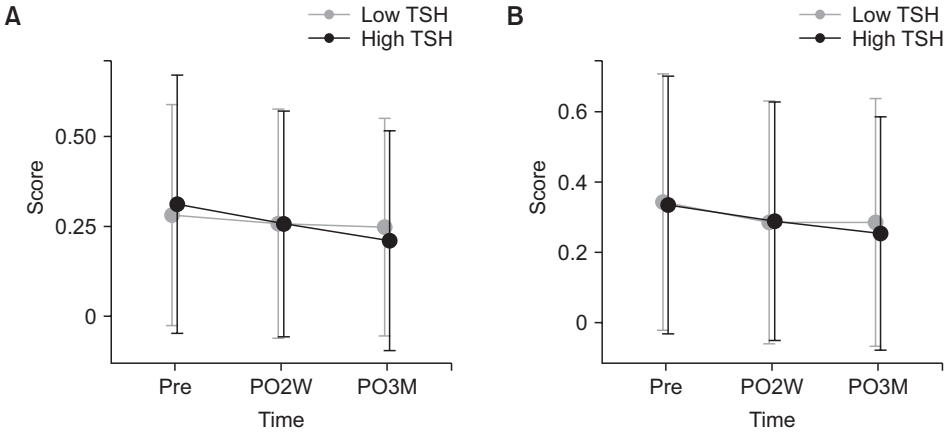

Fig. 3. Observed mean scores of the hyperthyroidism symptom scale (A) and Patient Health Questionnaire-9 (depression scores) (B). TSH, thyroid-stimulating hormone; Pre, preoperative; PO2W, postoperative 2 weeks; PO3M, postoperative 3 months.

Table 6. Fixed effects table for the linear mixed-effects model of HSS and PHQ-9 scores

Variable	HSS			PHQ-9		
	Estimates	95% CI	P-value	Estimates	95% CI	P-value
(Intercept)	0.31	–0.01 to 0.64	0.061	0.33	–0.07 to 0.72	0.105
Age	–0.00	–0.01 to –0.00	0.018*	–0.00	–0.00 to 0.00	0.134
Male sex (*vs*. female)	–0.08	–0.15 to –0.02	0.014*	–0.12	–0.20 to –0.04	0.002*
Smoking						
Past smoker (*vs*. nonsmoker)	0.00	–0.09 to 0.09	0.968	0.02	–0.09 to 0.13	0.667
Current smoker (*vs*. nonsmoker)	0.14	0.04 to 0.25	0.009*	0.19	0.07 to 0.32	0.003*
Comorbidity (*vs*. none)	0.07	0.01 to 0.12	0.013*	0.09	0.03 to 0.15	0.006*
Treatment group, high-TSH (*vs*. low-TSH)	–0.06	–0.53 to 0.41	0.809	–0.13	–0.70 to 0.44	0.663
PO3M fT4	0.07	–0.18 to 0.31	0.587	0.11	–0.18 to 0.41	0.453
Time						
PO2W (*vs*. Pre)	–0.13	–0.41 to 0.15	0.356	–0.23	–0.58 to 0.12	0.194
PO3M (*vs*. Pre)	–0.27	–0.55 to 0.01	0.060	–0.27	–0.62 to 0.09	0.139
Interaction terms						
High-TSH × PO3M fT4	0.06	–0.33 to 0.46	0.754	0.07	–0.42 to 0.55	0.789
High-TSH × PO2W	0.15	–0.30 to 0.60	0.519	0.41	–0.15 to 0.98	0.150
High-TSH × PO3M	0.32	–0.12 to 0.77	0.157	0.46	–0.11 to 1.02	0.112
PO3M fT4 × PO2W	0.08	–0.14 to 0.30	0.473	0.13	–0.15 to 0.42	0.345
PO3M fT4 × PO3M	0.18	–0.04 to 0.41	0.114	0.15	–0.14 to 0.43	0.312
High-TSH × PO3M fT4 × PO2W	–0.13	–0.50 to 0.25	0.506	–0.32	–0.79 to 0.15	0.183
High-TSH × PO3M fT4 × PO3M	–0.28	–0.66 to 0.09	0.142	–0.35	–0.83 to 0.12	0.142

HSS, hyperthyroidism symptom scale; PHQ-9, Patient Health Questionnaire-9 (depression scores); CI, confidence interval; TSH, thyroid-stimulating hormone; PO3M, postoperative 3 months; fT4, free thyroxine; PO2W, postoperative 2 weeks.
*P < 0.05.

L decreased from 82.3% at postoperative 3–6 months to 59.9% after 2 years of surgery. Therefore, patients may require the highest dosages of LT4 during postoperative 3–6 months when the TSH suppression target is set to <2 mIU/L, potentially resulting in a decline of HR-QoL. As both HR-QoL deterioration and TSH levels are at their highest at 3–6 months after thyroidectomy [20,23], this short-term interim analysis of HR-QoL changes in TL patients may provide valuable information to assist therapeutic planning. Moreover, since TSH is the most sensitive marker among thyroid hormones [24], it may offer a more precise assessment of patients' hormonal status by taking remnant thyroid function into consideration, as opposed to relying exclusively on LT4 dosages while assessing HR-QoL.

This study was performed as an intention-to-treat analysis considering the practical difficulty of satisfying the target TSH range by PO3M. Our results showed that mean TSH levels in the low-TSH group were slightly above 2 mIU/L at PO3M, and the TSH difference between the groups was not statistically significant. This may be due to the wide range of TSH levels which would have been affected by baseline thyroid functions,

as shown in our analysis of positive correlation between preoperative and PO3M TSH levels. However, the hormonal status of the 2 groups was still different at PO3M, as the low-TSH group had significantly higher fT4 and markedly lower TSH levels than the high-TSH group. The intention-to-treat analysis, therefore, was conducted as a reflection of real clinical practice for targeting TSH <2 mIU/L within 3 months. However, subsequent studies on long-term HR-QoL changes would need to consider per-protocol analysis to fully understand the effect of TSH suppression on HR-QoL.

TSH levels may have directly affected the physical status of patients, as we found better PO3M physical HR-QoL scores in the high-TSH group. In fact, TSH is involved in various physiological processes, such as muscle metabolism, glucose tolerance, and protection against osteoporosis, and studies have shown positive effects of TSH levels on physical function [25]. Samuels et al. [26] showed that in LT4-treated hypothyroidism patients, the lower normal TSH group (mean TSH, 1.85 mU/L) had lower physical function scores than the upper normal TSH group (mean TSH, 3.93 mU/L), although the difference was not statistically significant after correction. Meanwhile, Kim et al. [27] found that healthy men with lower TSH levels tended to have worse hand grip strength, especially those with a TSH level <1.44 mIU/L. There is a physiological basis for these associations since osteoblasts, osteoclast precursors, and skeletal muscle cells all express TSH receptors [25,28]. Deng et al. [29] demonstrated that rat osteoblasts treated with TSH proliferated at their maximum on the 5th day, accompanied by increased alkaline phosphatase and bone morphogenetic protein 2 expressions within 48 hours of TSH exposure, which are genes associated with osteoblast functionality. This rapid proliferation and differentiation of osteoblast treated with TSH may therefore account for the short-term improvement in physical HR-QoL. However, future studies are necessary to support this proposition.

This study also showed that psychological HR-QoL scores improved after surgery, possibly because we focused on low- to intermediate-risk thyroid cancer patients who underwent TL. Ryu et al. [14] also showed that psychological and spiritual HR-QoL scores improved postoperatively in TL patients. These findings may reflect the reduced psychological burden of cancer diagnosis after successful surgery. Moreover, previous studies have also shown that a cancer diagnosis itself results in lower patient QoL, implying that preoperative HR-QoL scores in our subjects may have been lower than the prediagnosis levels [30]. The psychological domain questions cover difficulties in overcoming the disease and fear of future diagnostics tests, recurrence, and metastases. Since this study excluded high-risk patients who were in need of completion thyroidectomy, any worries about disease status would have been assuaged at the time of the postoperative surveys, resulting in improved psychological HR-QoL. Low complication rates in our cohort may also have positively affected the total HR-QoL score, as well.

There are several limitations to our study. First, as shown in Table 1, compliance rates for answering questionnaires were low as some patients omitted questionnaires at certain time points. We thus used a linear mixed model for statistical analysis as it allows for missing values for analyzing serial measurements. Second, evaluation of socioeconomic status and marital stage was not included in the study design while these are important variables to consider in a HR-QoL study. Third, KT-QoL studies based on the healthy Korean population were not available, and thus whether HR-QoL psychological scores in low- to intermediate-risk thyroid cancer patients improved to prediagnosis levels could not be evaluated.

HR-QoL was not generally affected by postoperative TSH levels, except for the physical domain, in which HR-QoL was significantly higher after 3 months of surgery in patients who did not receive TSH suppression. Psychological HR-QoL improved in all patients, probably due to the successful resolution of the disease. Therefore, targeting TSH levels to <2 μIU/mL may need reconsidering if it does not have oncologic benefits as it may impair physical function after TL in the short-term postoperative period. As this study was an interim analysis, future analysis of long-term follow-up data is required to fully understand how TSH suppression affects postoperative HR-QoL changes in TL patients.

SUPPLEMENTARY MATERIALS

Supplementary Table 1 and Supplementary Fig. 1 can be found via https://doi.org/10.4174/astr.2024.106.1.19.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016;26:1-133.
2. McLeod DS, Sawka AM, Cooper DS. Controversies in primary treatment of low-risk papillary thyroid cancer. Lancet 2013;381:1046-57.
3. Patel KN. The year in thyroidology: surgical science. Thyroid 2023;33:21-3.
4. Lee MC, Kim MJ, Choi HS, Cho SW, Lee GH, Park YJ, et al. Postoperative thyroid-stimulating hormone levels did not affect recurrence after thyroid lobectomy in patients with papillary thyroid cancer. Endocrinol Metab (Seoul) 2019;34:150-7.
5. Jonklaas J, Sarlis NJ, Litofsky D, Ain KB, Bigos ST, Brierley JD, et al. Outcomes of patients with differentiated thyroid carcinoma following initial therapy. Thyroid 2006;16:1229-42.
6. Carhill AA, Litofsky DR, Ross DS, Jonklaas J, Cooper DS, Brierley JD, et al. Long-Term outcomes following therapy in differentiated thyroid carcinoma: NTCTCS Registry analysis 1987-2012. J Clin Endocrinol Metab 2015;100:3270-9.
7. Park S, Kim WG, Han M, Jeon MJ, Kwon H, Kim M, et al. Thyrotropin suppressive therapy for low-risk small thyroid cancer: a propensity score-matched cohort study. Thyroid 2017;27:1164-70.
8. Tagay S, Herpertz S, Langkafel M, Erim Y, Freudenberg L, Schöpper N, et al. Health-related quality of life, anxiety and depression in thyroid cancer patients under short-term hypothyroidism and TSH-suppressive levothyroxine treatment. Eur J Endocrinol 2005;153:755-63.
9. Grani G, Ramundo V, Verrienti A, Sponziello M, Durante C. Thyroid hormone therapy in differentiated thyroid cancer. Endocrine 2019;66:43-50.
10. Yaniv D, Vainer I, Amir I, Robenshtok E, Hirsch D, Watt T, et al. Quality of life following lobectomy versus total thyroidectomy is significantly related to hypothyroidism. J Surg Oncol 2022;126:640-8.

11. Monzani ML, Piccinini F, Boselli G, Corleto R, Margiotta G, Peeters RP, et al. Changes in quality of life after thyroidectomy in subjects with thyroid cancer in relation to the dose of levothyroxine. J Endocrinol Invest 2023;46:319-26.
12. Lee EK, Kang YE, Park YJ, Koo BS, Chung KW, Ku EJ, et al. A multicenter, randomized, controlled trial for assessing the usefulness of suppressing thyroid stimulating hormone target levels after thyroid lobectomy in low to intermediate risk thyroid cancer patients (MASTER): a study protocol. Endocrinol Metab (Seoul) 2021;36:574-81.
13. Dow KH, Ferrell BR, Anello C. Quality-of-life changes in patients with thyroid cancer after withdrawal of thyroid hormone therapy. Thyroid 1997;7:613-9.
14. Ryu CH, Park B, Ryu J, Ryu YM, Jo SA, Lee YJ, et al. Development and evaluation of a Korean version of a Thyroid-Specific Quality-of-Life Questionnaire Scale in thyroid cancer patients. Cancer Res Treat 2018;50:405-15.
15. Klein I, Trzepacz PT, Roberts M, Levey GS. Symptom rating scale for assessing hyperthyroidism. Arch Intern Med 1988;148:387-90.
16. Lee JE, Lee DH, Oh TJ, Kim KM, Choi SH, Lim S, et al. Validity and reliability of the Korean version of the Hyperthyroidism Symptom Scale. Endocrinol Metab (Seoul) 2018;33:70-8.
17. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16:606-13.
18. Park SJ, Choi HR, Choi JH, Kim KW, Hong JP. Reliability and validity of the Korean version of the Patient Health Questionnaire-9 (PHQ-9). Anxiety Mood 2010;6:119-24.
19. Goldfarb M, Casillas J. Thyroid cancer-specific quality of life and health-related quality of life in young adult thyroid cancer survivors. Thyroid 2016;26:923-32.
20. Chen W, Li J, Peng S, Hong S, Xu H, Lin B, et al. Association of total thyroidectomy or thyroid lobectomy with the quality of life in patients with differentiated thyroid cancer with low to intermediate risk of recurrence. JAMA Surg 2022;157:200-9.
21. Moon JH, Ryu CH, Cho SW, Choi JY, Chung EJ, Hah JH, et al. Effect of initial treatment choice on 2-year quality of life in patients with low-risk papillary thyroid microcarcinoma. J Clin Endocrinol Metab 2021;106:724-35.
22. Dou Y, Chen Y, Hu D, Su X. The recovery of thyroid function in low-risk papillary thyroid cancer after lobectomy: a 3-year follow-up study. Front Endocrinol (Lausanne) 2021;11:619841.
23. Bae MR, Nam SH, Roh JL, Choi SH, Nam SY, Kim SY. Thyroid stimulating hormone suppression and recurrence after thyroid lobectomy for papillary thyroid carcinoma. Endocrine 2022;75:487-94.
24. Sheehan MT. Biochemical testing of the thyroid: TSH is the best and, oftentimes, only test needed: a review for primary care. Clin Med Res 2016;14:83-92.
25. Abe E, Marians RC, Yu W, Wu XB, Ando T, Li Y, et al. TSH is a negative regulator of skeletal remodeling. Cell 2003;115:151-62.
26. Samuels MH, Kolobova I, Niederhausen M, Janowsky JS, Schuff KG. Effects of altering levothyroxine (L-T4) doses on quality of life, mood, and cognition in L-T4 treated subjects. J Clin Endocrinol Metab 2018;103:1997-2008.
27. Kim BJ, Lee SH, Isales CM, Hamrick MW, Kwak MK, Koh JM. Association of serum TSH with handgrip strength in community-dwelling euthyroid elderly. J Clin Endocrinol Metab 2018;103:3986-92.
28. Moon MK, Kang GH, Kim HH, Han SK, Koo YD, Cho SW, et al. Thyroid-stimulating hormone improves insulin sensitivity in skeletal muscle cells via cAMP/PKA/CREB pathway-dependent upregulation of insulin receptor substrate-1 expression. Mol Cell Endocrinol 2016;436:50-8.
29. Deng T, Zhang W, Zhang Y, Zhang M, Huan Z, Yu C, et al. Thyroid-stimulating hormone decreases the risk of osteoporosis by regulating osteoblast proliferation and differentiation. BMC Endocr Disord 2021;21:49.
30. Crevenna R, Zettinig G, Keilani M, Posch M, Schmidinger M, Pirich C, et al. Quality of life in patients with non-metastatic differentiated thyroid cancer under thyroxine supplementation therapy. Support Care Cancer 2003;11:597-603.