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# Thyroid-Stimulating Hormone as a Biomarker for Stress After Thyroid Surgery: A Prospective Cohort Study

Authors' Contribution:

Study Design A

Data Collection B

Statistical Analysis C

Data Interpretation D

Manuscript Preparation E

Literature Search F

Funds Collection G

AB **Hua Hong** 

ADE **Jeonghun Lee**

Department of Surgery, Ajou University Hospital, Suwon, South Korea

**Corresponding Author:** Jeonghun Lee, e-mail: [servent-lee@hanmail.net](mailto:servent-lee@hanmail.net)

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**Background:** Thyroid-stimulating hormone (TSH), which is regulated by the negative feedback of triiodothyronine (T3) and thyroxine (T4), is affected by cortisol (a stress hormone) and cytokines during allostasis. Thus, we assessed changes in TSH levels under stress and its potential as a stress marker in patients lacking T3 or T4 feedback after thyroid surgery.

**Material/Methods:** Three stress questionnaires (Korean version of the Daily Stress Inventory, Social Readjustment Rating Scale, and Stress Overload Scale-Short [SOSS]), an open-ended questionnaire (OQ), and thyroid function tests were administered twice to 106 patients enrolled from January 2019 to October 2020.

**Results:** In a multiple generalized linear mixed-effect model (GLMM) involving 106 patients, the T3 and free T4 levels, OQ, body weight, extent of thyroidectomy, and preoperative TSH levels were significantly correlated with log-transformed TSH (lnTSH). The modified SOSS (category) based on recent stressors on OQ interview was significantly associated with lnTSH. In the GLMM with modified SOSS (category), the lnTSH increased by 2.3 and 0.56 in the unconscious high- and high-risk groups, respectively, compared to that in the low-risk group ( $P < 0.05$ ). The calculated power of this study was 0.92 based on  $\alpha = 0.05$ .

**Conclusions:** TSH had a significant relationship with stress and the extent of thyroidectomy. An OQ supported the SOSS to help detect unrecognized stressors. TSH has potential utility as a stress marker combined with the modified SOSS (category) with sufficient power. However, questionnaires on social environments and research on coping strategies for stress are necessary for future studies.

**Keywords:** **Stress • Thyroid-Stimulating Hormone • Thyroidectomy • Thyroid Neoplasms**

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## Background

Thyroid-stimulating hormone (TSH) regulates thyroid hormones through feedforward control, whereas thyroid hormones control TSH via negative feedback to maintain a fixed thyroid hormone level [1]. The serum concentration of TSH is not constant and fluctuates over time, affected by the circadian rhythm, circannual rhythm, and pulsatile surge [2]. Furthermore, TSH levels increase with weight gain and decrease with aging [3,4]. TSH is also affected by cortisol in Cushing syndrome and cytokines in inflammation [5,6]. Although TSH must be kept constant, being a regulator of homeostasis, it is affected by external and internal environments.

Stress, defined as the nonspecific result of any demand on the body, affects the hypothalamus–pituitary–adrenal gland system, which also maintains homeostasis [7]. Stressful circumstances or stressors can influence the hypothalamus-pituitary-thyroid (HPT) axis, as well as psychological and physiological responses. TSH and free thyroxine (T4) levels decrease during starvation and depression in healthy people without thyroid disease, while these increase during obesity, cold, and psychosis [8]. In contrast, TSH can increase during depression, with elevated TSH levels making the treatment of depression difficult [9]. Therefore, even under the same stress conditions, TSH levels may vary from person to person.

In addition, stress exacerbates autoimmune thyroid diseases, such as Graves' disease and Hashimoto's thyroiditis, leading to elevated thyroid hormone and decreased TSH levels [10]. Despite being exposed to a similar stressor, autoimmune thyroid disease can make it difficult to interpret the response of the HPT axis.

In this study, the association between TSH and a stress questionnaire was evaluated in patients with absent or reduced thyroid capacity following thyroid surgery, and the usefulness of TSH as a stress marker was investigated.

## Material and Methods

### Ethics Statement

This study was approved by the Institutional Review Board of Ajou University Hospital (AJIRB-MED-SUR-19-045). All patients signed an informed consent form.

### Patients

This study was a single-center cohort study conducted from January 2019 to October 2020. Patients who underwent thyroidectomy and were followed-up regularly during the study period were included. Patients who refused to participate in

the self-administered questionnaire or were unable to fill out the questionnaire were excluded. After thyroid surgery, follow-up visits were usually scheduled every 2-3 months for the first year, and then every 6-12 months after 1 year. Following completion of the informed consent form and stress questionnaires, an interview with an endocrinological surgeon was conducted. An open-ended inquiry during the interview validated the category of recent stress.

Following a routine visit to our hospital, the mean period between surgery and administration of the first questionnaire was 51 months (range, 2-134 months). The mean period between the administration of the first and second questionnaires was 6.8 months (range, 4-12 months). The questionnaires were administered twice from January 2019 to October 2020.

### Data Collection

During the outpatient follow-up, data on demographic information, medical records of the operation and pathology, scores from the 3 questionnaires, responses to the items of the open-ended questionnaire, and serological thyroid function test results including TSH and free T4 and triiodothyronine (T3) were collected.

### Sample Size

Although this study initially planned to enroll 100 consecutive patients at the outpatient clinic, 106 were finally selected, expecting a 6% dropout rate.

### Korean version of Daily Stress Inventory (KDSI)

The Daily Living Stress Rating Scale (DSI) allows us to understand the role of stress in chronic diseases with fluctuating symptoms over time and the association between minor life events and physical and psychological symptoms. It also enables us to better understand the relationship between minor life events and the cause of the disease and more objectively evaluates the course of the disease and the therapeutic effect through a daily evaluation process [11].

The KDSI consists of 58 ordinary and minor events that can be encountered in daily life, with each being graded on a 7-point scale. These are classified into 5 groups according to the type or structure of the stressor [11]: interpersonal problems (12 items), personal competency (10 items), cognitive stressors (5 items), environmental stressors (14 items), and varied stressors (17 items).

### Social Readjustment Rating Scale (SRRS)

The Korean version of the SRRS was derived from that by Holmes and Rahe, which quantifies the amount of time and

effort required to return to the original state of psychophysiological instability caused by life changes in the past year [12]. The SRRS assigns magnitudes to each of the 42 life change items according to the amount, severity, and duration of adjustment required.

### Stress Overload Scale-Short (SOSS)

The stress overload scale has been shown to accurately predict pathological stress responses [13]. This 30-item scale is too long for clinical application. Thus, the 10-item SOSS was created. The SOSS assesses how much stress people felt the week before. It consists of 5 measures: event load (EL), which measure perceived pressures (such as “felt swamped by my tasks”), and 5 items called personal vulnerability (PV), which measure perceived weakness (such as “felt like just giving up”). Each item is 5-point reaction scale, with 1 denoting a very little response and 5 denoting a large one [13].

An oblique factor solution was used to produce the EL and PV scales, which were then correlated. The scale scores were added to produce 1 continuous score (range, 10-50) or categorical scores were made by creating a 2×2 matrix by dividing the sum of the scores by the mean: “High Risk” (high EL, high PV), “Low Risk” (low EL, low PV), “Challenged” (high EL, low PV), or “Fragile” (low EL, high PV) [13].

Continuous scores are not fully consistent with categorical scores; an individual with a middle-range sum could be classified as “High Risk” or another category based on where their scores fall in relation to EV or PV. In a population sample, categorical ratings showed excellent sensitivity (96%) and specificity (100%) in distinguishing stressed and symptomatic people [13]. The Korean version of the SOSS was used for the enrolled patients.

### Open-Ended Questionnaire (OQ)

After completing the questionnaires, individuals were asked if they had experienced any lifestyle changes or life events since their last outpatient appointment. Patients with high TSH levels were asked if they were regularly taking levothyroxine or if they were taking it with other medications or meals.

### Statistics

SPSS 25 (IBM Corp., Armonk, N.Y., USA) was used for reliability analysis of the SOSS and correlation with other stress questionnaires, and a generalized linear mixed-effect model (GLMM) was performed using R software version 4.1.2 (R Core Team, Vienna, Austria). A *P* value less than 0.05 was considered to be statistically significant. The sample size and power were calculated using R software version 4.1.2 [14].

## Results

### Baseline Characteristics

The average age of the enrolled patients was 46 years, and the male-to-female ratio was 1: 3.8. Total thyroidectomy was performed in 88 patients (83.9%), and 89 patients received levothyroxine (83.9%). Four patients did not have T stage information because they underwent surgery at a different hospital. The N stage information was absent in 9 patients who underwent surgery at a different hospital or did not have lymph node dissection. Eleven patients (10.4%) underwent modified radical neck dissection. Fifteen patients experienced a significant life event, with 8 in the first period and 7 in the second (**Table 1**).

### SOSS

The SOSS had a Cronbach's value of 0.944, indicating a high level of internal agreement. The Cronbach's alpha value (0.935-0.941) did not change significantly when the individual items were excluded (**Table 2**). In terms of validity, the correlation between the SOSS, KDSI, and SRRS was high in the correlation analysis (**Table 3**).

### GLMM

In the univariate GLMM, T3, free T4, OQ stress event, N stage, and the extent of thyroidectomy were associated with lnTSH (natural logarithm) (**Table 4**). TSH levels did not correlate with any of the other stress questionnaires.

Multiple GLMM included the statistically significant covariates in all patients, along with sex, age, and body weight, which are already known to be correlated with TSH. Preoperative TSH was not significant in the univariate analysis but was included in the multiple analyses to reduce confounding effects caused by chronic disease before the study period. Among the categories of the SOSS, there were 4 individuals who had experienced life events despite being segregated in the low-risk group (**Table 5**); therefore, the multiple analysis was performed after relocating these cases into the unconscious high-risk group.

The GLMM model 1, including the significant factors of sex, age, body weight, modified SOSS (category) and preoperative TSH, and modified SOSS (category), significantly correlated with lnTSH, T3, free T4, body weight, and the extent of thyroidectomy. However, sex and age were not significant factors. After analyzing the GLMM, including the significant factors in model 1, we found that the modified SOSS (category) was still a significant factor related to ln TSH. In model 2, lnTSH increased by 2.3 and 0.56 in the unconscious high- and high-risk groups, respectively, compared to that in the low-risk group ( $P<0.05$ ) (**Table 6**). The calculated sample size for a future study was 60 patients

**Table 1.** Characteristics of the enrolled patients.

Characteristics		Values
Age	Mean±SD	46.7±9.84
Height	Mean±SD	163.4±7.23
Body weight (kg) 1 <sup>st</sup>	Mean±SD	63.5±11.76
Body weight (kg) 2 <sup>nd</sup>		63.6±11.26
Sex	Male	22 (20.8%)
	Female	84 (79.2%)
Approach	Open	88 (83%)
	Robotic/endoscopic	17 (16%)
Extent of thyroid surgery	Total	58 (54.7%)
	Less than total	48 (45.3%)
Levothyroxine 1 <sup>st</sup>	Medication (Mean±SD, µg)	89 (113±30.4)
	No medication	17 (16.0%)
Levothyroxine 2 <sup>nd</sup>	Medication (Mean±SD, µg)	89 (108.1±32.7)
	No medication	17 (16.0%)
Pathology	Papillary cancer	102 (96.2%)
	Follicular cancer	1 (0.9%)
	Medullary cancer	1 (0.9%)
	Benign goiter	2 (1.9%)
Tumor size (cm)	Mean±SD (mm)	10.3±7.86
T stage (%)	T1	84 (79.2%)
	T2	7 (6.6%)
	T3	8 (7.5%)
	T4	3 (2.8%)
	Tx	4 (3.8%)
N stage (%)	N0	58 (54.7%)
	N1a	28 (26.4%)
	N1b	11 (10.4%)
	Nx	9 (8.5%)
M stage (%)	M0	105 (99.1%)
	M1	1 (0.9%)
Preoperative TSH	Mean±SD (µIU/mL)	2.8±7.13
TSH 1 <sup>st</sup>	Mean±SD	2.7±5.63
TSH 2 <sup>nd</sup>	Mean±SD	2.6±7.68
Free T4 1 <sup>st</sup>	Mean±SD (ng/dL)	1.34±0.28
Free T4 2 <sup>nd</sup>	Mean±SD	1.44±0.24

**Table 1 continued.** Characteristics of the enrolled patients.

Characteristics		Values	
T3 1 <sup>st</sup>		Mean±SD (ng/dL)	99.9±17.7
T3 2 <sup>nd</sup>		Mean±SD	102.5±15.35
KDSI 1 <sup>st</sup>		Mean±SD (ng/dL)	94.2±78.61
KDSI 2 <sup>nd</sup>		Mean±SD	91.5±71.82
SOSS 1 <sup>st</sup>		Mean±SD (ng/dL)	20.2±10.88
SOSS 2 <sup>nd</sup>		Mean±SD	18.6±9.49
SRRS 1 <sup>st</sup>		Mean±SD (ng/dL)	148.2±108.03
SRRS 2 <sup>nd</sup>		Mean±SD	109.8±102.22
Stress event			
1 <sup>st</sup> period		Cases (%)	8 (7.5%)
2 <sup>nd</sup> period		Cases (%)	7 (6.6%)
SOSS (category)		1 <sup>st</sup>	2 <sup>nd</sup>
Low risk, cases (%)		73 (68.9%)	79 (74.5%)
Challenge		0	2 (1.9%)
Fragile		11 (10.4%)	20 (8.5%)
High risk		22 (20.8%)	38 (15.1%)
Life event, stress	Distress	Change in work hours	2 (13.3%)
		Personal illness	1 (6.6%)
		Change in sleeping habits	1 (6.6%)
		Death of close family member	2 (13.3%)
		Business readjustment	3 (20%)
		Trouble with in-laws	1 (6.6%)
		Trouble with boss	1 (6.6%)
		Other stress	3 (20%)
	Eustress	Change in recreation	1 (6.6%)

KDSI – Korean version of Daily Stress Inventory; TSH – thyroid stimulating hormone; SD – standard deviation; SRRS – Social Readjustment Rating Scale; SOSS – Stress Overload Scale-Short.

based on the 4 groups of modified SOSS (category),  $\alpha=0.05$ , power=0.8, and a 5% dropout rate through GLMM using R software (version 4.1.2). Additionally, the power of 106 patients was 0.92 based on modified SOSS (category) and  $\alpha=0.05$  using GLMM.

## Discussion

The fluctuations in the TSH levels were found to be influenced by stress, T3 and free T4, body weight, and the extent of thyroidectomy. As previously reported, T3 and free T4 have an

inverse relationship with TSH, and TSH is low in patients who have undergone total thyroidectomy because they received T4 suppression therapy for advanced cancer. When analyzing the modified SOSS (category) based on the OQ, the TSH levels increased when the risk of stress increased or when there was a stressful event. Additionally, the power of this study was sufficient to support the results (power=0.92).

The HPT axis, along with the hypothalamus-pituitary-adrenal gland axis, plays a critical role in homeostasis. They work synergistically to control energy balance and influence each other.

**Table 2.** Internal consistency analysis of the Korean SOSS.

Item	Scale mean if item deleted	Corrected item-total correlation	Cronbach's alpha if item deleted
1	18.02	0.687	0.941
2	17.42	0.739	0.940
3	17.89	0.762	0.938
4	17.74	0.715	0.940
5	17.94	0.805	0.937
6	17.86	0.833	0.935
7	18.17	0.777	0.938
8	17.78	0.783	0.937
9	18.16	0.758	0.939
10	17.78	0.833	0.935

**Table 3.** Correlation between each stress questionnaire.

	SOSS 1 <sup>st</sup>		SOSS 2 <sup>nd</sup>		
	Coefficient	p-value	Coefficient	p-value	
KDSI 1 <sup>st</sup>	0.397	<0.001	KDSI 2 <sup>nd</sup>	0.368	<0.001
SRSS 1 <sup>st</sup>	0.538	<0.001	SRSS 2 <sup>nd</sup>	0.475	<0.001

This has been previously reported in patients with Cushing syndrome and hyperthyroidism [15,16]. Therefore, changes in cortisol levels during stress can impact the TSH level. Although TSH has potential as a stress marker, it had a few limitations in this study because it did not reflect the questionnaires frequently used as stress-measuring tools. In our study, the KDSI, SOSS (continuous value), and SRRS did not show any correlation with the TSH levels.

This discrepancy between the endocrine system and questionnaires was also observed for cortisol, a well-known stress marker [17]. This issue is caused by daily cortisol fluctuations. TSH, like cortisol, also has a circadian and circannual cycle and exhibits 8-12 pulsatile rhythms per day [18]. In addition, this discrepancy may be attributed to the difference in reaction time to external stressful stimuli under negative feedback of thyroid hormones on the hypothalamus–pituitary axis. The HPT axis is repressed during T4 suppression after thyroid surgery, and it takes more than 2 months for the HPT axis to recover. When the HPT axis is normal, it is known to respond to external stressful stimuli within minutes [19]. This means that, depending on how much HPT axis suppression following thyroid surgery has been restored, individuals with T4 suppression may have a delayed response time or a low level of response to a

stressful event. To resolve this disagreement between TSH and the questionnaires, TSH levels should be measured repeatedly to calculate the area under the curve of TSH levels, just as repeated measurements of cortisol levels and the area under the curve of cortisol levels solve the disparity between cortisol levels and questionnaires [20].

As suggested by previous studies examining the relationship between stress and disease [21-24], the discrepancy between endocrine function and subjective stress is also attributed to unmeasured confounding factors, such as memory recall, coping strategies, personality variables, emotional regulation strategies, social support, uncontrollable environmental factors, or a dynamic system between the individual's psychological functions and the environmental stimulus [25-27]. In this study, there were 4 cases in the low-risk group of SOSS, but an OQ interview revealed elevated TSH levels and a recent life event. After placing them in the category of unconscious high-risk group, it was possible to confirm the association between TSH and the questionnaire. These unconscious stressors may have contributed to the difference between TSH and other questionnaires. It is presumed that the various confounding factors mentioned above may have influenced the failure of the unconscious high-risk group to recognize recent life events as

**Table 4.** Univariate linear mixed-effect regression in all enrolled patients.

Variable	lnTSH			P-value
	Estimate	95% CI		
Sex (female)	-0.011	-0.856	0.834	0.9787
Age	0.028	-0.007	0.063	0.1259
Body weight	0.021	-0.009	0.051	0.1608
Height	-0.011	-0.058	0.036	0.6432
T3	-0.058	-0.073	-0.043	< 0.0001
Free T4	-4.895	-5.749	-4.041	< 0.0001
Stress event (present)	3.203	2.169	4.237	< 0.0001
KDSI	0.000	-0.004	0.004	0.8781
SOSS	0.003	-0.026	0.032	0.8390
SOSS-category				
High vs low	0.192	-0.499	0.883	0.584
Challenge vs low	0.496	-0.454	1.446	0.304
Fragile vs low	-0.221	-1.219	0.776	0.662
SRRS	-0.001	-0.004	0.002	0.7215
Body weight, during operation	0.018	-0.010	0.046	0.2157
N stage				
N1a vs N0	-0.260	-1.037	0.517	0.5131
N1b vs N0	-1.243	-2.359	-0.127	0.0313
Extent of thyroidectomy (total)	-1.552	-2.178	-0.926	<0.0001
Approach (robotic/endoscopic)	0.620	-0.327	1.567	0.2019
Preoperative TSH	0.031	-0.022	0.084	0.246

stressors. It is believed that measuring these confounding factors in future studies will aid in more accurate identification of the relationship between TSH and stress.

In this study, various confounding factors could not be investigated, but the OQ was able to make up for these limitations. When the TSH and questionnaire scores differ, the problem of unmeasured confounding factors can be compensated for to some extent by using an OQ as a backup alternative. The characteristics of the category classification of SOSS may have contributed to the association between TSH and stress, which was also due to the characteristics of the category classification of SOSS. The continuous scores of SOSS are not fully redundant with categorical scores; an individual with a middle-range total score could be classified as “High Risk” or another category depending on where their scores fall in relation to the meaning of the scale. Due to the procedure of producing

categorical scores, confounding factors that were not measured in the analysis of the total score of the SOSS could be corrected.

The other characteristic feature of this study is that the response of the hypothalamus–pituitary axis to stress can be confirmed when the target organ of TSH has insufficient or no reserves due to thyroid surgery. The TSH, T3, and T4 levels show different patterns depending on the allostatic load in a person with a normal thyroid reserve. For example, during depression, TSH levels either increase or remain normal, but T3 and T4 levels decrease, and in anxiety, the TSH level is either low or normal, and T3 and T4 levels increase [28]. However, Panicker et al reported that TSH levels increased in patients taking L-thyroxine for hypothyroidism regardless of depression and anxiety [29]. In our study, the hypothalamus–pituitary axis was kept hyperactive regardless of the type of stress in patients that underwent thyroid surgery. In other words, in

**Table 5.** Classification of patients based on the SOSS category and OQ.

Period	SOSS		Life event on OQ	
	Category	Absent	Present	
1 <sup>st</sup> period	Low	50	1	
	Fragile	10	2	
	Challenge	11	2	
	High	27	3	
	Total	98	8	
2 <sup>nd</sup> period	Low	53	3	
	Fragile	6	2	
	Challenge	11	0	
	High	29	2	
	Total	99	7	
Types of life event in a low-risk group		Insomnia Increased frequency of climbing Change of occupation		

**Table 6.** Multiple linear mixed-effect regression in all enrolled patients.

	Model 1		Model 2	
	Estimate	p-value	Estimate	p-value
Sex (female)	0.623	0.125	–	–
Age	-0.017	0.221	–	–
Body weight	0.039	0.006	0.041	0.003
T3	-0.033	<0.001	-0.029	<0.001
Free T4	-3.483	<0.001	-3.431	<0.001
N stage				
N1a vs N0	-0.103	0.723	–	–
N1b vs N0	-0.404	0.349	–	–
Extent of thyroidectomy (total)	-1.053	<0.001	-0.903	0.001
Preoperative TSH	0.047	0.012	0.044	0.019
SOSS (category)			–	–
Unconscious high vs low	2.266	0.001	2.338	0.001
High vs low	0.339	0.206	0.566	0.026
Challenged vs low	0.131	0.718	0.301	0.391
Fragile vs low	-0.256	0.518	-0.241	0.527



people with a normal reserve of thyroid, the anticipated allostatics will occur as a consequence of the harmony of T3 and T4 secretion, deiodinase activity, coping strategies, emotional regulation strategies, and so on. If the thyroid reserve is not sufficient to secrete thyroid hormone, hyperactivity of the hypothalamus-pituitary axis may persist under stress.

This study had a small sample size, and a large-scale study that assesses thyroid function and numerous stress questionnaires repeatedly is needed.

## Conclusions

TSH had a significant relationship with stress, together with T3, T4, preoperative TSH, and the extent of thyroidectomy. The

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