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Original Research

Relationship Between Thyroid-Stimulating Hormone Level and Aggressive Pathological Features of Papillary Thyroid Cancer

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Abstract

Objectives: Thyroid-stimulating hormones (TSHs) are associated with the risk of differentiated thyroid cancer. The relationship between pre-operative TSH levels and aggressive features is unclear. We aimed to evaluate the relationship between pathological features of papillary thyroid carcinoma (PTC) and high TSH levels.

Methods: Patients who were operated between 2012 and 2017 and who were found to have PTC in their pathology were included in the study. The relationship between TSH and the features of tumor aggressiveness was evaluated in the patients.

Results: Of the 132 patients, TSH level was significantly higher in those with lymphovascular invasion than those without (p=0.048), in those with central metastases than in those without (p=0.014), and in those with extrathyroidal spread than in those without (p=0.003). When patients were categorized into four 25% quartiles according to TSH (mUI/mL) level; the rate of extrathyroidal invasion increased as the TSH level increased, and the level was significantly higher in quartile 1 than the others, with significant difference (p=0.030).

Conclusion: Pre-operative increase in TSH level is associated with an increased risk of extrathyroidal spread and central lymph node metastasis. TSH level may be a pre-operative valuable predictive factor for patients' risk of central metastasis.

Keywords: Papillary thyroid cancer; thyroid-stimulating hormone; thyroidectomy.

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Thyroid cancer has an increasing incidence due to the increase in diagnostic imaging modalities. Papillary thyroid carcinoma (PTC) is the most common differentiated thyroid cancer (DTC).[1] However, the etiology has not been clarified much, except for reasons such as age, a history of radiation to the neck region, and a previous history of PTC, which predispose to DTC.[2]

Thyroid-stimulating hormone (TSH) is the main regulator and growth factor of the thyroid. Since it is the major hormone stimulating thyrocytes, increased serum concentrations of TSH have been found to be associated with cancer risk in thyroid nodules.[3,4] The basis of this view is that TSH has an effect on the proliferation of malignantly transformed DTC cells, as well as on thyrocytes. TSH has been

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found to be important in the development of human DTC both in animal models and in observational studies, but there is still no conclusive evidence.[2,5]

TSH suppression therapy is associated with increased prognosis in high-risk thyroid cancers.[6]

PTC tends to metastasize especially to regional lymph nodes, and the incidence of lymph node metastasis is reported to be between 30 and 80%. Lymph node metastasis primarily occurs in the central region, and the power of pre-operative radiological imaging methods to detect central metastasis is limited. The aggressive features of the tumor are thought to be associated with metastasis, especially lymph node metastasis.[7]

For this reason, it is important to predict preoperatively pathologically aggressive tumor features that may have a significant impact on clinical outcomes.[8]

It is not possible to predict most of the pathological features preoperatively. The relationship of these pathological features with pre-operative biochemical examinations may contribute significantly to the planning of the patient's treatment. The relationship of TSH at the time of diagnosis with the prognostic aggressive features of the tumor is not clear. Studies on this subject are limited.[9,10] The data to be obtained in this regard may contribute to the determination of the surgical extent of the patients, the post-operative risk classification, and the planning of the treatment.

In this study, we aimed to evaluate the relationship between the aggressive clinicopathological features of PTC and high TSH levels.

Methods

Before the study, the permission of the local Ethics Committee (Date: 24/11/2020, Number: 3019) was obtained. Our study was conducted in accordance with the Declaration of Helsinki.

The data of patients who were operated by a single surgeon between 2012 and 2017 and PTC was detected in the pathological examinations of the specimens which were evaluated retrospectively. Patients with cancers other than PTC and patients with pathology reports and/or pre-operative TSH levels which could not be reached were excluded from the study. The pre-operative TSH relationship with the presence of tumor aggressive clinicopathological features such as male gender, being over 55 years of age, tumor size over 1 cm, tumor T stage, multicentricity, lymphovascular invasion, central lymph node metastasis, lateral lymph node metastasis, and extrathyroidal spread, was evaluated in the patients in the study.

Statistical Analysis

Statistical analysis was performed with IBM SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL, USA). For descriptive statistics, numbers and percentages were calculated for categorical variables, mean, standard deviation, and minimum and maximum values were calculated for numerical variables. Since the numerical variables did not meet the normal distribution condition, two groups were compared using the Mann–Whitney U-test. The ratios in the groups were compared with Chi-square analysis. Multinomial logistic regression analysis was used to analyze predictive TSH values and categories. Risk parameters among quartiles were evaluated with odds ratio (OR) and 95% confidence. Statistical alpha significance level was accepted as $p<0.05$.

Results

A total of 132 patients with PTC (103 F and 29 M) with a mean age of 46.4±13.6 years were included in the study. TSH level (mean±standard deviation) of the patients was 1.81±1.57 mUI/mL. When patients were divided into four quartiles according to TSH value, TSH levels were found as >2.36 mUI/mL in quartile 1, 1.44–2.35 mUI/mL in quartile 2, 0.69–1.43 mUI/mL in quartile 3, and <0.68 mUI/mL in quartile 4.

Among the evaluated features, the pre-operative TSH level was higher in patients with lymphovascular invasion than without (2.22±1.63 mUI/mL vs. 1.68±1.56 mUI/mL, p=0.048) (Table 1). However, when the patients were evaluated according to the quartiles, although the lymphovascular invasion rate increased as the TSH level increased, the difference between the groups was not statistically significant (quartile 1: 36.4%, quartile 2: 27.3%, quartile 3: 21.2%, and quartile 4: 15.2%; p=0.222) (Table 2).

It was found to be significantly higher in patients with central lymph node metastases than in those without (2.32±1.47 mUI/mL vs. 1.71±1.59 mUI/mL, p=0.014) (Table 1). When the patients were evaluated according to four quartiles, although the presence of central metastases from tumor aggressiveness characteristics was not statistically significant (close to the significance limit [p=0.055]), the rate of central metastases increased as TSH value increased, and the rates in quartiles were as follows: 36.4% in quartile 1, 36.4% in quartile 2, 22.7% in quartile 3, and 4.5% in quartile 4 (Table 2).

It was found to be significantly higher in patients with extrathyroidal spread than in those without (2.31±1.55 mUI/mL vs. 1.61±1.56 mUI/mL; p=0.003, respectively) (Table 1). The rate of extrathyroidal invasion increased as the TSH value increased, significantly higher in quartile 1 than the

Table 1. TSH (mUI/mL) values according to clinical and pathological features

	TSH (mUI/mL)	p
Age/year		
<55	1.92±1.64	0.192
>55	1.46±1.29	
Gender		
Female	1.79±1.58	0.813
Male	1.85±1.55	
Tumor size		
<1 cm	1.84±1.68	0.781
>1 cm	1.70±1.42	
T stage		
T1+2	1.74±1.54	0.368
T3	3.07±2.13	
Multicentricity		
Present	1.76±1.43	0.922
Absent	1.87±1.71	
Lymphovascular invasion		
Present	2.22±1.63	0.048
Absent	1.68±1.56	
Central metastasis		
Present	2.32±1.47	0.014
Absent	1.71±1.59	
Lateral metastasis		
Present	2.12±1.61	0.263
Absent	1.77±1.58	
Extrathyroidal spread		
Present	2.31±1.55	0.003
Absent	1.61±1.56	

TSH: Thyroid-stimulating hormone.

others, and the difference was also significant (quartile 1: 42.1%, quartile 2: 23.7%, quartile 3: 18.4%, and quartile 4: 15.8%; p=0.030) (Table 2).

There was no statistically significant difference in TSH levels and aggressive clinicopathological features (age, gender, tumor size, multicentricity, number of foci, and presence of lateral metastases) in terms of patient rates according to TSH categories.

In the multinomial logistic regression analysis, taking the category 4 as reference group, the risk of extrathyroidal spread was approximately 4-fold in quartile 1 (OR: 4.167, p=0.013), and the risk of central metastasis was approximately 11-fold in quartile 2 (OR:10.909, p=0.029) and was 10-fold higher in quartile 1 (OR:10, p=0.036). Although the risk of lymphovascular invasion was approximately 3 times higher in quartile 1 than in quartile 4 (OR: 3.120, p=0.062), the difference was not significant (Table 3).

Discussion

Although increased TSH serum concentration has been shown to be associated with cancer risk in thyroid nodules,[3,4] the effect of TSH on carcinogenesis and cancer biology is still unclear.[10]

In our study, we evaluated the clinicopathological features associated with TSH level and aggressiveness of PTC. TSH level of PTC in those with lymphovascular invasion was significantly higher in those without (2.22±1.63 mUI/mL vs. 1.68±1.56 mUI/mL, p=0.048), in those with central lymph node metastasis than in those without (2.32±1.47 mUI/mL vs. 1.71±1.59 mUI/mL, p=0.014), was significantly higher in those with extrathyroidal extension than in those without (2.31±1.55 vs. 1.61±1.56; p=0.003).

Lymphatic invasion of the tumor in PTC leads to multifocal lesion in the thyroid gland and metastases in regional lymph nodes, while vascular invasion leads to the development of metastases outside the neck.[11,12]

In our study, the rate of lymphovascular invasion increased as TSH level increased, while lymphovascular invasion was 15.2% in patients with TSH <0.68 mUI/mL (quartile 4), 36.4% in patients with TSH >2.36 mUI/mL (quartile 1), and the difference between the quartiles was not statistically significant (p=0.222) (Table 2). In addition, the risk of lymphovascular invasion was approximately 3 times higher in quartile 1 compared to quartile 4 (OR: 3.120, p=0.062), and although the difference was not significant, it was close to the limit of significance. Although the rate of central metastases increased as the TSH level increased when compared in quartiles (quartile 1:36.4%, quartile 2: 36.4%, quartile 3: 22.7%, and quartile 4: 4.5%; p=0.055), the difference was close to significance. However, when patients were divided into quartiles, the risk of central metastasis in quartile 2 (1.44–2.35 mUI/mL) was approximately 11-fold (OR:10.909, p=0.029) and was 10-fold (OR:10, p=0.036) in quartile 1 (TSH >2.36 mUI/mL), when quartile 4 was taken as reference group (<0.68 mUI/mL). The rate of extrathyroidal invasion increased with increased TSH value, and the difference was significant and was significantly higher in quartile 1 than in other quartiles (quartile 1: 42.1%, quartile 2: 23.7%, quartile 3: 18.4%, and quartile 4: 15.8%; p=0.030). Compared to quartile 4, the risk of extrathyroidal spread was approximately 4 times higher in quartile 1 (OR: 4.167, p=0.013, Table 3). The number of studies evaluating the relationship between clinicopathological features and TSH is limited in the literature. TSH level was found to be an independent predictive factor for extrathyroidal spread and central metastasis in PTC in one study,[9] and an independent predictive factor for extrathyroidal spread and lateral metastasis in DTC in another study.[13]

Table 2. Comparison of tumor aggressiveness rates between 25% quartiles according to TSH level

	TSH (mUI/mL)				
	Quartile 1 (>2.36 mUI/mL) (%)	Quartile 2 (1.44–2.35 mUI/mL) (%)	Quartile 3 (0.69–1.43 mUI/mL) (%)	Quartile 4 (<0.68 mUI/mL) (%)	p
Age (n=132)					0.160
<55	29 (29)	22 (22)	26 (26)	23 (23)	
>55	4 (12.5)	10 (31.3)	8 (25)	10 (31.3)	
Gender (n=132)					0.950
Female	25 (24.3)	26 (25.2)	26(25.2)	26 (25.2)	
Male	8 (27.6)	6 (20.7)	8 (27.6)	7 (24.1)	
Tumor size (n=126)					0.504
<1 cm	18 (25.4)	19 (26.8)	15 (21.1)	19 (26.8)	
>1 cm	13 (23.6)	11 (20)	18 (32.7)	13 (23.6)	
T stage (n=126)					0.083
T1+2	30 (24.6)	27 (22.1)	33 (27)	32 (26.2)	
T3	1 (25)	3 (75)	0	0	
Multicentricity (n=126)					0.978
Present	14 (24.6)	13 (22.8)	15 (26.3)	15 826.3)	
Absent	18 (26.1)	17 (24.6)	18 (26.1)	16 (23.2)	
Lymphovascular invasion (n=126)					0.222
Present	12 (36.4)	9 (27.3)	7 (21.2)	5 (15.2)	
Absent	20 (21.5)	21 (22.6)	26 (28)	26 (28)	
Central metastasis (n=127)					0.055
Present	8 (36.4)	8 (36.4)	5 (22.7)	1 (4.5)	
Absent	24 (22.9)	22 (21)	29 (27.6)	30 (28.6)	
Lateral metastasis (n=129)					0.602
Present	5 (31.3)	5 (31.3)	4 (25)	2 (12.5)	
Absent	28 (24.8)	25 (22.1)	30 (26.5)	30 (26.5)	
Extrathyroidal spread (n=126)					0.030
Present	16 (42.1)	9 (23.7)	7 (18.4)	6 (15.8)	
Absent	16 (18.2)	21 (23.9)	26 (29.5)	25 (28.4)	

TSH: Thyroid-stimulating hormone.

Table 3. Relationship between clinicopathological aggressiveness and TSH in PTC according to TSH quartiles

	TSH (mUI/mL)						
	Quartile 1		Quartile 2		Quartile 3		Quartile 4
	OR (%95 CI)	P	OR (%95 CI)	P	OR (%95 CI)	P	Reference
Age >55	0.317 (0.088–1.143)	0.079	1.045 (0.365–2.998)	0.934	0.708 (0.239–2.096)	0.533	1
Tumor size >1 cm	1.056 (0.387–2.879)	0.916	0.846 (0.304–2.357)	0.749	1.754 (0.656–4.689)	0.263	1
Multicentricity (±)	0.830 (0.308–2.237)	0.712	0.816 (0.297–2.237)	0.692	0.889 (0.333–2.375)	0.814	1
Lymphovascular invasion (±)	3.120 (0.944–10.308)	0.062	2.229 (0.648–7.664)	0.204	1.400 (0.393–4.985)	0.604	1
Central LNM (±)	10 (1.168–85.594)	0.036	10.909 (1.270–93.692)	0.029	5.172 (0.569–47.003)	0.144	1
Lateral LNM (±)	2.679 (0.480–14.941)	0.261	3.000 (0.535–16.814)	0.212	2 (0.340–11.756)	0.443	1
Extrathyroidal spread (±)	4.167 (1.348–12.882)	0.013	1.786 (0.546–5.839)	0.337	1.122 (0.331–3.803)	0.854	1

OR: Odds ratio; %95 CI: %95 confidence interval; LNM: Lymph node metastasis; TSH: Thyroid-stimulating hormone; PTC: Papillary thyroid carcinoma.

Other studies have shown that the rate of central metastasis is high, especially in the presence of pathological features such as extrathyroidal spread, multifocality, lymphovascular invasion, and capsular invasion.[14,15]

Li et al.[16] evaluated the prognostic role of TSH and serum thyroid autoantibodies (thyroglobulin antibody [TgAb] and thyroid microsomal antibody [TMAb]) in DTC. In multivariance analysis, TgAb was determined as an independent predictive factor for >1 cm tumor, and TSH level and TgAb>1 for central metastasis.

In another study, the relationship between tumor size of <1 cm and >1 cm and clinicopathological factors in PTC was evaluated, and multicentricity, lymphovascular invasion, extrathyroidal spread, central lymph node metastasis, and lateral lymph node metastasis were found to be higher in tumors of >1 cm. However, pre-operative TSH, TgAb, and TMAb levels were found to be similar in tumors <1 cm and >1 cm.[17] In our study, there was no significant difference between pre-operative TSH level and age, gender, T stage, tumor size (<1 cm vs. >1 cm), and lateral metastasis.

The thyroid-stimulating hormone receptor (TSHR) is a surface glycoprotein receptor and is expressed in both benign and malignant thyrocytes. More than 20 years ago, it was started to be defined that in DTCs, TSHRs of the surface receptor decrease due to the decrease in mRNA level, and that there is an inverse correlation between the mRNA level of these receptors and cancer aggressiveness.[18] An increase in serum TSH is observed in DTC due to decreased expression of the TSHR surface receptor. Therefore, it is suggested that pre-operative increased TSH levels are associated with PTC in terms of prognosis.[19]

Although the relationship between TSH and PTC has not been clearly defined, it has been clearly demonstrated that TSH suppression therapy gives positive results in high-risk patients and advanced cancers.[6]

Zheng et al.[20] evaluated 20,227 thyroid cancer patients from 56 different studies in their meta-analysis and found that TSH level was effective on nodule diameter and lymph node metastasis. However, in some studies, no relationship was found between TSH level and central lymph node metastasis.[21] Due to TSH increasing the proliferation of thyrocytes, it is possible for malignant thyrocytes to metastasize to the central neck region, where they will first spread.

On the other hand, there are studies reporting that TSH level is not associated with poor prognostic factors in patients with advanced PTC.[22] However, many studies in the literature emphasize that TSH has a progressive effect on DTC and report that TSH suppression therapy has satisfactory results, especially in early-stage DTCs.[6,20]

The limitations of our study are that it has a retrospective design, not all histopathological features have been recorded in some patients, and long-term follow-ups have not been evaluated. It was not specified whether the extracapsular spread was minimal or extensive, as it was not mentioned in the pathology reports. Moreover, all the aggressive pathological features of papillary thyroid cancer could not be included in the study. However, we think that the results of this study will contribute significantly to the literature, since there are limited studies on this subject in the literature.

Conclusion

Some aggressive pathological features of PTC may be related to pre-operative TSH. An increase in TSH level is associated with an increased risk of extrathyroidal spread and central lymph node metastasis. TSH level may be a valuable pre-operative predictive factor for patients' risk of central metastasis.

Disclosures

Ethics Committee Approval: Şişli Hamidiye Etfal Training and Research Hospital Local Ethics Commitee (Date: 24/11/2020, Number: 3019).

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