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The Relationship Between TSH Level and Stage of Differentiated Thyroid Carcinoma

Diferansiye Tiroid Karsinomunun Evresi ile TSH Düzeyi Arasındaki İlişki

Esra TUNÇEZ, Mustafa KULAKSIZOĞLU*, İsmail Hakkı TUNÇEZ**

Konya Education Research Hospital, Konya, TURKEY
*Necmettin Erbakan University Meram Faculty of Medicine, Department of Internal Medicine, Konya, TURKEY
**Konya Provincial Health Directorate, Konya, TURKEY

Abstract

Objective: The aim of this study was to determine whether thyroid-stimulating hormone (TSH) levels during the diagnosis of patients with differentiated thyroid carcinoma could be used for the prediction of cancer behavior. **Material and Methods:** The records of 329 patients with differentiated thyroid carcinoma who did not use levothyroxine at the time of diagnosis were reviewed retrospectively. The demographic and clinical characteristics of the cases and serum TSH levels were recorded at the time of diagnosis and statistically analyzed. **Results:** A total of 329 cases with 322 papillary carcinomas and 7 follicular carcinomas were included in the study. The median age of the participants at the time of diagnosis was 45 (17-76) years. Eighty-three percent of the cases were diagnosed in stage 1, 6.7% in stage 2, 3.3% in stage 3, and 7.0% in stage 4. The median serum TSH level at the time of diagnosis of the cases was 1.34 (0.01-9.97) mIU/mL. We did not observe any statistically significant relationship between the serum TSH level and the stage of differentiated thyroid carcinoma, although higher serum TSH level was associated with lymph node metastasis and higher risk group in the American Thyroid Association (ATA) classification. **Conclusion:** The relationship between serum TSH level and thyroid cancer has not been clearly determined, but high TSH levels at the time of diagnosis were found to be associated with lymph node metastasis and medium-high ATA risk score.

Keywords: Thyroid cancer; tumor burden; lymphatic metastasis; neoplasm staging

Özet

Amaç: Bu çalışmanın amacı, diferansiye tiroid karsinomlu hastaların tanı anındaki tiroid stimüle edici hormon (TSH) düzeylerinin kanser davranışını tahmin etmek için kullanılıp kullanılamayacağını belirlemekti. **Gereç ve Yöntemler:** Çalışmada tanı anında levotiroksin kullanmayan diferansiye tiroid karsinomlu 329 hastanın kayıtları retrospektif olarak incelendi. Olguların demografik ve klinik özellikleri ile tanı anındaki serum TSH düzeyleri kaydedildi ve istatistiksel olarak analiz edildi. **Bulgular:** Çalışmaya, toplam 329 (322'si papiller, 7'si foliküler karsinomlu) olgu dâhil edildi. Katılımcıların tanı anındaki ortanca yaşı 45 (17-76) yıl idi. Olguların %83'ü evre 1, %6,7'si evre 2, %3,3'ü evre 3 ve %7,0'ı evre 4 olarak teşhis edildi. Olguların tanı anında medyan serum TSH düzeyi 1,34 (0,01-9,97) mIU/mL idi. Serum TSH düzeyi ile diferansiye tiroid karsinomunun evresi arasında istatistiksel olarak anlamlı bir ilişki gözlemlemedik, ancak yüksek serum TSH düzeyi, "American Thyroid Association (ATA)" sınıflandırmasına göre lenf nodu metastazı ile ilişkili bulunmuştur. **Sonuç:** Serum TSH düzeyi ile tiroid kanseri arasındaki ilişki net olarak belirlenmemiştir, ancak tanı anındaki yüksek TSH düzeyleri lenf nodu metastazı ve orta-yüksek ATA risk skoru ile ilişkili bulunmuştur.

Anahtar kelimeler: Tiroid kanseri; tümör yükü; lenfatik metastaz; tümör evrelemesi

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Address for Correspondence: Esra TUNÇEZ, Konya Education Research Hospital, Konya, TURKEY
Phone: +90544 347 11 11 **E-mail:** dr.esra88@hotmail.com

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Introduction

Thyroid cancers account for about 1% of all malignancies and are the most common malignancy of the endocrine system. The incidence of thyroid cancer, which has been reported to be 2-3/100,000 individuals worldwide in the last century, has witnessed a 2 to 5-fold increase in the last 20 years (1). In Turkey, according to the data of 2014 Cancer Statistics, the incidence of thyroid cancer was 20.7/100,000 in women and 5.5/100,000 in men (2). In countries where iodine intake is sufficient, 95% of thyroid cancers are differentiated thyroid carcinoma (DTC), and among these, papillary cancers constitute the majority (3).

For DTC staging, several scoring systems such as MACIS, MSKCC, AMES, EORTC, and TNM are used. The most commonly used TNM Classification of Malignant Tumors (TNM) staging system developed by the American Joint Committee on Cancer is staging based on tumor size, lymph node, and distant metastasis. However, the TNM classification does not fully evaluate the risk factors and recurrence associated with thyroid cancer; therefore, a separate risk scoring system was developed by the American Thyroid Association (ATA), grouped as low, moderate, and high risk (4).

Thyroid-stimulating hormone (TSH), growth factors, and some cytokines are primarily responsible for the growth of the thyroid gland (5). TSH receptor is expressed on the DTC cell membrane, and TSH stimulation increases the synthesis and growth of proteins such as thyroglobulin and increases the activity of sodium-iodine symporter (6). The underlying mechanism for thyroid hyperplasia is chronic stimulation caused by slightly elevated TSH levels, which may lead to carcinomatous changes in the case of iodine deficiency (4). Long-term TSH stimulation is known to contribute to neoplastic growth and a worse prognosis (7).

In this study, the effect of TSH on thyroid gland growth was examined, and any possible relationship between the level of TSH at the time of diagnosis and the aggression of cancer in DTC patients was determined.

Material and Methods

Case Features

Between January 2006 and January 2016, a total of 329 cases were diagnosed for pathological DTC in the Necmettin Erbakan University Meram Medical Faculty of Endocrinology and Metabolic Diseases Department. The data of the patients were retrospectively evaluated. The inclusion criteria were a new histopathological diagnosis of DTC, and age 18 years or older. The exclusion criteria were a history of use of levothyroxine therapy and insufficient data. Approval was obtained from Necmettin Erbakan University Meram Medical Faculty, Ethics Committee for Drug and Non-Medical Device Research (No:2016/572/33) for the study and it was carried out in accordance with the patient rights regulation of the Helsinki Declaration. Cases were evaluated by examining identification information, laboratory results, pathology reports, and radiology reports from the hospital automation systems. Sex, age, cancer types, histopathological subtypes of cancer, serum TSH levels at the time of diagnosis, tumor diameters, lymph node metastases, distant metastases, and tumor multifocality situations were recorded. Patients' TNM cancer stages and ATA risk scores were also determined. The relationship between serum TSH level at the time of diagnosis and tumor diameters, lymph node metastasis, tumor multifocality, TNM stages, and ATA risk scores were analyzed statistically.

Statistical Analysis

The data obtained from the research were statistically analyzed by IBM SPSS 23.0 (IBM SPSS Statistics, Version 23.0 Armonk, NY: IBM Corp.). Descriptive statistics are provided using the median (minimum-maximum) and percentage distribution. Normality analysis was performed by the Kolmogorov-Smirnov test. Kruskal-Wallis variance analysis was used to compare continuous data between multiple groups, and the Mann-Whitney U test was used to compare between two groups. Pearson's correlation analysis was used to determine the relationship between numerical data. A p-value of <0.05 was accepted for statistical significance.

Results

Among the 329 cases included in the study, 261 (79.3%) were female, and 68 (20.7%) were male. The median age of the participants at the time of diagnosis was estimated to be 45 (18-76) years; 155 (47.1%) cases were under 45 years of age, and 174 (52.9%) were 45 years and older.

Three hundred twenty-two (97.9%) patients had papillary carcinoma and 7 (2.1%) had follicular carcinoma. The median tumor diameter was 1.2 (0.1-12) cm. In addition, among 322 papillary carcinoma cases, 126 (39.1%) cases were microcarcinomas. Additionally, 120 (36.5%) cases had multifocal tumors. At the time of diagnosis, the number of cases without lymph node metastasis was 276 (83.9%), and the number of cases with lymph node metastasis was 53 (16.1%). Only 1 (0.3%) case had distant metastasis, and no distant metastasis was detected in the remaining 328 (99.7%) cases at the time of diagnosis.

Considering the TNM staging at the time of diagnosis, 273 (83.0%) cases were in stage 1, 22 (6.7%) were in stage 2, 11 (3.3%) were in stage 3, 19 (5.8%) were in stage 4A, 3 (0.9%) were in stage 4B, and one (0.3%) case was in stage 4C. According to the risk classification, 232 (70.5%) cases were in the low-risk group, 93 (28.3%) cases were in the intermediate-risk group, and four (1.2%) cases were in the high-risk group. The distribution of the histopathological subtypes of the tumors and other tumor characteristics are shown in Table 1.

The median serum TSH levels at the time of diagnosis were found to be 1.34 (0.01-9.97) mIU/mL. The distribution of serum TSH level of the participants is presented in Figure 1.

No statistically significant correlation was observed between the tumor diameters at the time of diagnosis and serum TSH levels (p=0.300). The distribution and correlation curve of serum TSH levels based on tumor diameters are presented in Figure 2.

Table 2 presents the median serum TSH levels according to the presence of lymph node metastasis, ATA risk score, tumor multifocality status, and TNM stages. Serum TSH level at the time of diagnosis was found to be significantly higher in patients with lymph

Table 1. Some tumor characteristics of differentiated thyroid carcinoma cases.

		n (%)
Cancer type	Papillary carcinoma	322 (97.9)
	Follicular carcinoma	7 (2.1)
	Classic type	239 (72.7)
Histopathological subtype	Follicular type	70 (21.3)
	Other	20 (6.0)
Tumor multifocality	No	209 (63.5)
	Yes	120 (36.5)
Lymph node metastasis	No	276 (83.9)
	Yes	53 (16.1)
Distant metastases	No	328 (99.7)
	Yes	1 (0.03)
	Stage 1	273 (83.0)
	Stage 2	22 (6.7)
TNM stage	Stage 3	11 (3.3)
	Stage 4A	19 (5.8)
	Stage 4B	3 (0.9)
	Stage 4C	1 (0.3)
	Low	232 (70.5)
ATA risk scores	Intermediate	93 (28.3)
	High	4 (1.2)
	Total	329 (100)

ATA: American Thyroid Association.

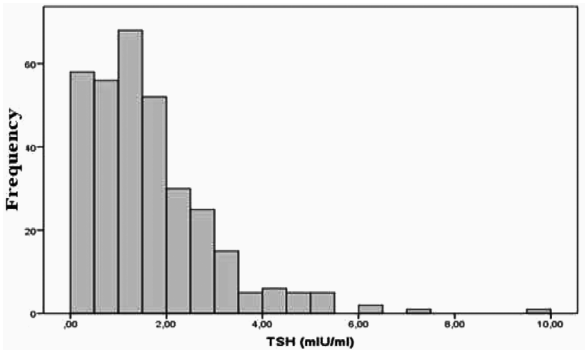

Figure 1: Distribution of serum thyroid-stimulating hormone (TSH) levels in patients with differentiated thyroid carcinoma.

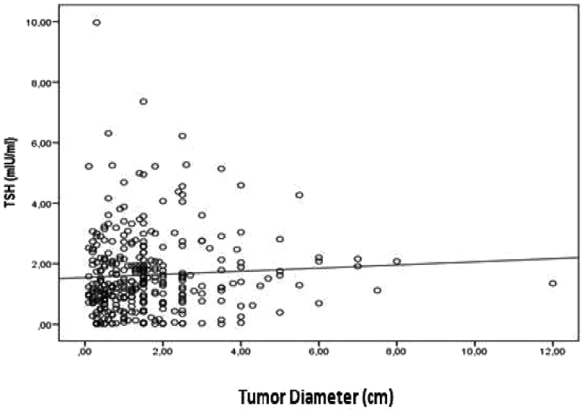

Figure 2: Distribution and correlation curves of thyroid-stimulating hormone (TSH) levels according to tumor diameters of patients with differentiated thyroid carcinoma.

node metastasis than those with non-lymph node metastases (p<0.001) and in patients with intermediate-high ATA risk than those with low risk (p=0.031). No statistically significant difference was observed between serum TSH levels at the time of diagnosis in patients with and without multifocal tumors (p=0.950). There was also no statistically significant difference between the serum TSH levels at the time of diagnosis according to the stage of the cases (p=0.052).

Discussion

The majority of thyroid cancers are DTCs with papillary and follicular subtypes. Donald et al. reported that 93.2% of patients with DTC had papillary thyroid carcinoma, and 6.8% had follicular thyroid carcinoma (8). In the current study, among 329 patients with DTC, 97.9% of the patients had papillary thyroid carcinoma, and 2.1% had follicular thyroid carcinoma.

In our study, 79.3% of the cases were female, and 20.7% were male. Likewise, in a study conducted by Mazurat et al. in 2013, including 2125 DTC cases, 76.6% of the patients were female, and 23.4% were male (9). In another study conducted by Lily et al. in 2012, including 55,995 DTC cases, 77.5% of the patients were female, and 22.5% were male (10). The earlier available reports indicated that thyroid cancers are 2-4 times more common in women than men.

Table 2. Serum TSH levels according to lymph node metastasis status, ATA risk score, tumor multifocality status and TNM stages of differential thyroid carcinoma cases.

		Serum TSH level (mIU/mL) Median (Range)	p
Lymph node metastasis	No	1.26 (0.01-9.97)	<0.001
	Yes	1.89 (0.05-6.22)	
ATA risk score	Low	1.25 (0.01-9.97)	0.031
	Intermediate-high	1.55 (0.01-6.22)	
Tumor multifocality	No	1.35 (0.01-9.97)	0.950
	Yes	1.31 (0.01-6.22)	
	Stage 1	1.37 (0.01-9.97)	
	Stage 2	0.69 (0.01-3.02)	
TNM stages	Stage 3	1.83 (0.53-4.38)	0.052
	Stage 4A	1.35 (0.05-4.56)	
	Stage 4B	2.08 (1.12-2.16)	
	Stage 4C	1.92 (1.92-1.92)	

TSH: Thyroid-stimulating hormone; ATA: American Thyroid Association.

Accordingly, in our study, the female/male ratio with DTC was found to be 3.83/1, like that in earlier literature.

Merhy et al. conducted a study in the USA and observed that the median age at diagnosis of DTC patients was 49 years (11). In this study, we found that the age of diagnosis was between 18 and 76 years and the median age of diagnosis was 45 years in accordance with the literature.

In earlier reports, the tumor diameter was found in the range of 0.1-12 cm and the median tumor diameter was 1.2 cm in our study. Pietro et al. conducted a study on 215 patients and reported a mean tumor diameter of 1.53 cm (12). In another study by Giovanni et al., the average tumor diameter was 1.36 cm (13). Papillary microcarcinomas with a tumor diameter of less than 1 cm constitute approximately 30% of all papillary cancers and are less aggressive (14,15). In our study, the rate of papillary microcarcinoma was 39.1%, which is higher than that reported in earlier studies.

In our study, tumor multifocality was found in 36.5% of the patients with DTC, and this rate is congruent with earlier reports. For instance, in the meta-analysis study published by Guo and Wang in 2014, this rate was estimated to be 36.6% (16).

We also classified the 329 cases according to TNM staging system and found that 83.0% of patients were in stage 1, 6.7% were in stage 2, 3.3% were in stage 3, 5.8% were in stage 4A, 0.9% were in stage 4B, and 0.3% were in stage 4C. In addition, at the time of diagnosis, 16.1% of the cases presented with lymph node metastasis, while only 0.3% of the cases presented with distant metastasis. In a study conducted by Kocak et al., 69.3% of the patients were found to be in stage 1, 23% in stage 2, 6.3% in stage 3, and 1.3% in stage 4 (17). In another study on 75 DTC cases, Karacavus et al. found that 21.6% of the patients had lymph node metastasis, and 9.5% had distant metastasis (18). While the incidence of lymph node metastasis in our study is congruent with the findings of earlier studies, the incidence of distant metastases in stage 1 patients is higher, and the incidence of distant metastasis is less than that reported in the literature; this can be attributed to the high rate of microcarcinoma cases in our study.

The patients in our study were categorized according to the ATA risk stratification system into low, intermediate, and high-risk groups. A total of 70.5% of the cases were in the low-risk group, 28.3% were in the intermediate-risk group, and 1.2% were in the high-risk group. Kocak et al. conducted a study on 300 patients with DTC and found that 54.7% of the patients were in low risk, 39.7% were in intermediate-risk, and 5.7% were in high-risk group (17), while Tuttle et al. studied 588 patients with DTC, and found that 23% of the patients were in low, 50% were in intermediate, and 27% in the high-risk groups (19). Deviating from earlier reports, more patients in our study were in the low-risk group. This can be attributed to the non-aggressive tumor behavior and low distant metastasis rate in the cases in this study.

Considering serum TSH levels, Tuna et al. conducted a study in 201 patients with DTC and found that their preoperative serum TSH level was in the range of 0.01-9.6 mIU/mL and median serum TSH level was 1.66 mIU/mL (20). In our study, serum TSH levels at the time of diagnosis were in the range of 0.01-9.97 mIU/mL, and the median serum TSH level was 1.34 mIU/mL.

We then investigated the relationship between serum TSH levels at the time of diagnosis and tumor size, tumor multifocal status, lymph node metastasis status, ATA risk score, and TNM stages. No statistically significant difference was found between serum TSH levels at the time of diagnosis according to the TNM staging of the cases. There was also no statistically significant correlation between tumor diameter and serum TSH levels. In addition, no statistically significant difference, based on the TSH level, was observed between the patients with and without multifocal tumors at the time of diagnosis. Similarly, Tuna et al. also reported that there was no correlation between tumor diameter and serum TSH levels, and that serum TSH levels did not change according to tumor multifocality or lymph node metastasis status (20). The findings of our study support the findings of Tuna's study in terms of tumor diameter and multifocality. However, we observed that serum TSH levels were significantly higher in patients with lymph node metastasis at

the time of diagnosis than those without lymph node metastasis. In addition, the serum TSH level at the time of diagnosis was significantly higher in moderate-high ATA risk group patients than in low ATA risk group patients.

Not many studies have investigated the relationship between thyroid cancer and serum TSH levels. Recently, Haymart et al., reported that high serum TSH level increased the incidence of thyroid cancer and also associated with advanced-stage cancer (21). In another study, the same researchers reported that high serum TSH levels related to the extrathyroidal spread of cancer (22). On the other hand, some studies report no correlation between serum TSH levels and the incidence of DTC and poor prognostic factors. For instance, in two different studies conducted by Kim et al., no significant relationship was observed between serum TSH level and tumor size (23,24). Likewise, we observed no direct correlation between serum TSH levels at the time of diagnosis and the stage of DTC.

This is one of the rare studies investigating the relationship between thyroid cancer and serum TSH level in our country. However, a limitation of this study is that the majority of patients had microcarcinomas and low-grade carcinomas.

Conclusion

Although no direct correlation was observed between serum TSH level and cancer stage, high serum TSH levels were found to be associated with the presence of lymph node metastasis, and high ATA risk group. The relationship between serum TSH level and thyroid cancer has not been clearly identified in the literature, and this deficiency should be overcome by repeating similar studies by determining the effect of TSH on thyroid cancer aggressiveness in more homogeneous case groups.

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Conflict of Interest

There are no conflicts of interest between the authors and/or family members of the scientific and medical committee members, or members of the potential conflicts of interest, counseling, expertise, working conditions, shareholding, and similar situations in any firm.

Authorship Contributions

Idea/Concept: Mustafa Kulaksızoğlu, Esra Tunçez; Design: Esra Tunçez; Control/Supervision: Mustafa Kulaksızoğlu; Data Collection and/or Processing: Esra Tunçez, İsmail Hakkı Tunçez; Analysis and/or Interpretation: Esra Tunçez, İsmail Hakkı Tunçez; Literature Review: Esra Tunçez; Writing the Article: Esra Tunçez; Critical Review: Mustafa Kulaksızoğlu; References and Fundings: Esra Tunçez; Materials: Esra Tunçez.

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