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# Diagnostic and Prognostic Value of TSH Levels in Differentiated Thyroid Cancers

## Diferansiye Tiroid Kanserinde TSH Düzeyinin Tanısal ve Prognostik Değeri

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### Abstract

**Purpose:** The frequency of thyroid surgery for suspected malignancy but with a benign result in pathological examination is increasing in recent years. For this reason, additional preoperative markers are needed for increasing the sensitivity for evaluating the preoperative malignancy risk of thyroid nodules. In this study, we aimed to evaluate the diagnostic value of serum TSH levels for determining the differentiated thyroid cancers (DTC) and to identify a proper cut-off value if relevant association is present.

**Material and Method:** Our study included 380 patients who underwent thyroidectomy due to nodular goiter in our hospital between 01.01.2012 and 01.06.2013 retrospectively. 201 patients who were diagnosed with DTC constituted the study group, and 179 consecutive patients with a benign pathology result were included as controls. Patients who had overt hyperthyroidism or hypothyroidism and was taken medicines that affect TSH level were excluded.

**Results:** There were no significant differences between the two groups in terms of age, sex, and family history of thyroid disease. Preoperative TSH levels were 1.66 mIU/lt and 1.59 mIU/lt in patients with DTC and controls, respectively (p=0.641). There was no correlation between TSH and tumor size, and no relationship between TSH and capsular invasion, vascular invasion, extrathyroidal invasion and lymph node metastasis.

**Discussion:** In our study, no relationship was found between preoperative TSH level and DTC. In addition, there was no relationship between TSH and bad prognostic parameters. *Turk Jem 2014; 1: 1-4*

**Keywords:** TSH, differantiated thyroid cancer, papillary cancer

### Özet

**Amaç:** Günümüzde giderek artan sıklıkta malignite şüphesi nedeni ile yapılan ancak patoloji sonucu benign saptanan tiroid operasyonları yapılmaktadır. Bu nedenle tiroid nodüllerinin preoperatif malignite riskini değerlendirmek için sitoloji ile birlikte duyarlılığını arttıracak ek preoperatif belirteçlere ihtiyaç duyulmaktadır. Bu çalışmada diferansiye tiroid karsinom tanısı alan hastaların preoperatif serum TSH düzeyinin diferansiye tiroid kanseri için tanısal değerini araştırmak ve anlamlı ilişki varsa uygun bir tanısal eşik değer saptamak amaçlanmıştır.

**Gereç ve Yöntem:** Çalışmamıza 01.01.2012- 01.06.2013 yılları arasında hastanemizde tiroidektomi yapılıp patoloji sonucu diferansiye tiroid kanseri (DTK) saptanan 201 hasta ve patoloji sonucu benign saptanan 179 birey kontrol grubu olarak dahil edildi. Aşikar hipotiroidi veya hipertiroidi olan hastalar ve tiroid fonksiyonlarını etkileyen ilaç tedavisi alan hastalar çalışma dışı bırakıldı.

**Bulgular:** Çalışmamıza alınan iki grup arasında yaş, cinsiyet ve ailede tiroid kanseri öyküsü açısından fark yoktu. Diferansiye tiroid kanseri olan hastalarda preoperatif TSH düzeyi (TSH: 1,66 mIU/lt) kontrol grubu (TSH: 1,59 mIU/lt) ile benzer saptandı (p=0,641). Ayrıca tiroid kanseri olan grupta TSH düzeyi ile tümör boyutu, kapsül invazyonu, damar invazyonu, ekstratiroidal yayılım ve lenf nodu tutulumu arasında ilişki saptanmadı.

**Tartışma:** Çalışmamızda TSH düzeyi ile DTK arasında ilişki bulunamamıştır. Ayrıca tiroid kanseri olan grupta TSH düzeyi ile kötü prognostik belirteçler arasında ilişki saptanmadı. *Turk Jem 2014; 1: 1-4*

**Anahtar Kelimeler:** TSH, differansiye tiroid kanseri, papiller kanser

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## Introduction

Thyroid cancer constitutes about 90% of endocrine system cancers, 1% of all cancers and 0.2% of cancer-related mortality, worldwide (1). Today, the number of operations for suspected malignancy but with a benign pathological result is increasing. Although fine needle aspiration (FNA) has a high sensitivity and specificity, high frequency of false-negative and inconclusive results cause unnecessary operations. One of the explanations for false negative results is incidental microcarcinomas. In a study by Gul K. at al., 83 of 224 (37%) patients with thyroid cancer were diagnosed incidentally (2). For this reason, additional preoperative markers are needed to increase the sensitivity of cytology for evaluating the preoperative malignancy risk of thyroid nodules. Differentiated thyroid cancers (DTC) express thyroid stimulant hormone (TSH) receptors and give response to TSH stimulation by this way (3). In addition, it is well known that TSH suppression treatment improves disease-free survival in high-risk patients with DTC (4). Recently, it has been reported that there is a relationship between TSH levels and DTC in patients with nodular thyroid diseases, and also, higher TSH values, despite within normal range, are associated with more advanced stage of DTC (5). The aim of this study was to evaluate diagnostic value of preoperative serum TSH concentrations for DTC in patients without overt hypo- or hyperthyroidism, and presence of a proper diagnostic cut-off value if a relevant association was found.

## Materials and Methods

### Patient Recruitment

Data of patients, who underwent total thyroidectomy or near total thyroidectomy for Graves' disease, nodulary or multinodulary goiter in Ankara Numune Education and Research Hospital between January 1, 2012 and June 1, 2013, were collected retrospectively. Patients who had undergone completion thyroidectomy and who were previously treated with radioiodine ablation were excluded from the study. Patients who used levothyroxine or antithyroid drugs, and diagnosed with poorly differentiated tumors or medullary thyroid cancer were also excluded. Patients with subclinical hypothyroidism or hyperthyroidism were included according to free thyroksin, free iodothyronin and TSH levels. But patients with overt hypothyroidism or overt hyperthyroidism were excluded. Results of remaining 201 patients who were found to have differentiated thyroid carcinoma (185 (92%) were with papillary thyroid carcinoma, 16 (8%) were with follicular thyroid carcinoma) were included as study group (group 1), and 179 consecutive patients with benign pathology results and meeting inclusion criteria were included as control group (group 2). Demographic characteristics of the patients (age, sex), histopathological characteristics of the tumor (dimensions, multifocality, bilaterality, extrathyroidal involvement, capsulary invasion, vasculary invasion and presence of cervical lymph node metastasis), and preoperative levels of serum TSH were analyzed.

### Laboratory Analyses

Laboratory analyses of TSH, fT3 and fT4 were performed by using Access HYPERsensitive human TSH, Access FT3 and Access FT4 assays, respectively, and by chemiluminescence method (Roche Diagnostics). Normal reference values for thyroid function tests were 0.34-4.25 µIU/ml, 2.5-3.9 pg/ml, and 0.61-1.2 pg/ml for TSH, fT3, and fT4, respectively

### Statistical Analyses

SPSS (Statistical Package for Social Sciences) for Windows 18.0 was used for statistical analyses of the data in this study. Normal distribution of the continuous data was tested by the Shapiro-Wilk test. Normally distributed continuous data were presented as mean ± standart deviations, non-normally distributed continuous data were presented as median (minimum-maximum), and categorical variables were presented as number of cases and (%). Significance of the difference of means were analyzed by the Student's t test, and significance of the difference of medians were analyzed by the Mann-Whitney U test between groups. Significance of the difference of categorical variables were analyzed by either Pearson's Chi-Square or Fisher's Exact Chi-Square tests. Pearson correlation coefficients were calculated for normally distributed variables. Significance level was accepted as 0.05, significant difference was called when $p<0.05$, and non-significant difference was called when $p>0.05$.

### Ethical Committee Approval

Local Ethics Committee of Ankara Numune Education and Research Hospital approved this study with 635/2013-approval number.

## Results

This study included data of 380 patients (319 females, 61 males) with a mean age of 46.7 (16-77) years. There were no significant differences between groups 1 and 2 for age, sex and mean TSH levels (Table 1). The mean tumor size was 11.8±11.2 mm (1-94) in patients with DTC. One-hundred and eight of patients had microcarcinoma (53.7%), and 93 of them had tumors over 10 mm in diameter (46.3%). There was no significant difference in distribution of patients with DTC between the age groups ($p=0.061$).

There was no correlation between TSH and tumor size ($r=-0.072$, $p=0.310$, Figure 1). Also no significant difference was found between TSH levels and groups according to the tumor dimensions (<5 mm, 5-10 mm, >10 mm) or micro- and macrocarcinomas (Table 2).

No significant differences was found between TSH levels of DTC patients with and without multifocality, capsulary invasion, vasculary invasion, extrathyroidal extension and lymph node

**Table 1. Demographic characteristics and TSH levels of groups**

| | Group 1 (n=201) | Group 2 (n=179) | p value |
|---|---|---|---|
| Age | 45.5±12.3 | 47.93±12.1 | 0.054 |
| Sex (M/F) | 170/ 31 | 149/ 30 | 0.433 |
| TSH (mIU/lt) | 1.66 (0.01-9.6) | 1.59 (0.02-9.1) | 0.641 |

metastasis (Table 3). Distant metastasis was found in none of the patients.

Subclinical hypothyroidism detected in 26 patients (14 patients were in group 1, 12 were in group 2) and subclinical hyperthyroidism detected in 75 patients (40 patients were in group 1, 35 were in group 2). Of this 75 patients, 52 were due to toxic multinodulary goiter and 23 were toxic diffuse goiter. DTC prevalence was not significantly different when grouped according to the TSH levels as subclinical hyperthyroidism (TSH range 0.01-0.4), euthyroidism (TSH range 0.4-4.4) and subclinical hypothyroidism (TSH range 4.5-9.6) (Figure 2). DTC/control ratio was 53.3%, 52.4% and 53.8% respectively (p=0.914). In our study, the association between TSH level and final histology remained nonsignificant after patients with subclinical hypo- and hyperthyroidism were excluded (p=0,256).

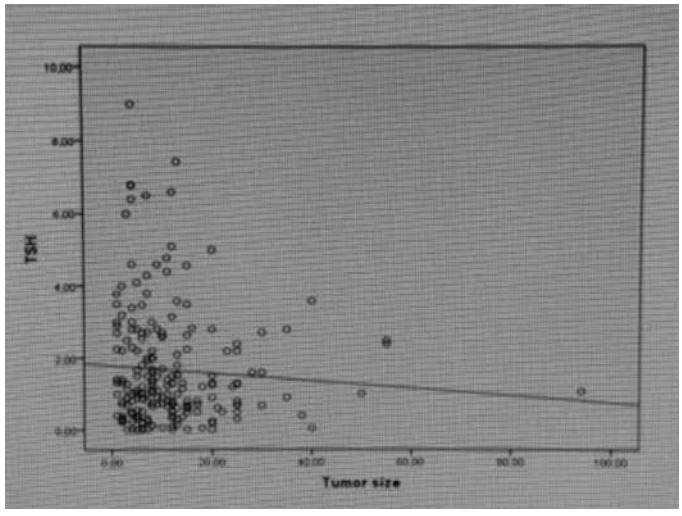


**Figure 1.** Correlation grafic between TSH and tumor size

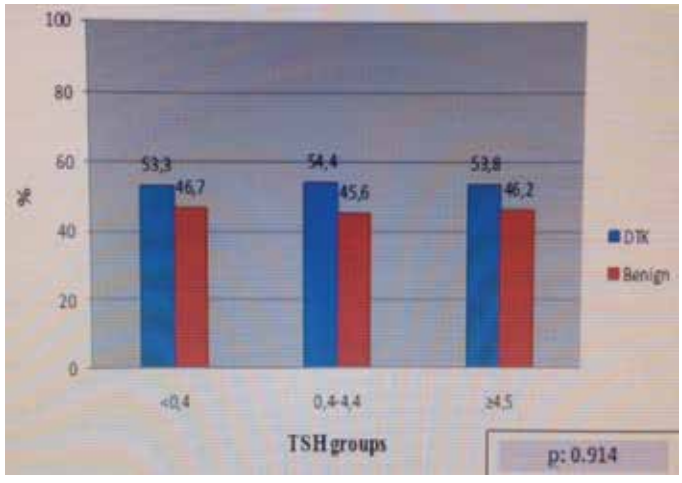


**Figure 2.** Proportion of patients with DTC according to TSH groups

**Table 2. Comparison of tumor dimensions and TSH**

| Tumor dimension | Number of patients | TSH (mIU/lt) Median (min-max) | p value |
|---|---|---|---|
| <5 mm | 47 | 2.14 (0.01-9.6) | 0.06 |
| 5-10 mm | 61 | 1.48 (0.01-6.5) | |
| >10 mm | 93 | 1.53 (0.03-8.6) | |
| 0-10 mm | 108 | 1.77 (0.01-9.6) | 0.32 |
| ≥10 mm | 93 | 1.53 (0.03-8.6) | |

## Discussion

Growth of thyroid gland is primarily provided by TSH, growth factors and some cytokines. Differentiated thyroid cancers express TSH receptors and give response to TSH stimulation by this way (3). It was shown in animal models that TSH may lead to thyroid cancer, but it was not proved that it is the main factor for thyroid cancers in humans (6). First study that showed the relationship between thyroid cancers and TSH levels was published in 2006 by Boalert et al. (7). Higher TSH levels were shown to be related with thyroid malignancy (risk of thyroid cancer in group with TSH levels lower than 0.4 mIU/lt was 2.4%, and 29.6% in group with TSH levels between 1.8 to 5.5, p<0.001). One of the limitations of this study is that classification was based on FNA biopsy results. The other limitation was that patients on levothyroksin or antithyroid drugs were not excluded. In 2012, Mcleod et al. published a meta-analysis including 22 studies, 5605 cancer cases and 40.929 controls. According to the results of this study thyroid cancer risk was two times higher in patients with TSH levels of 4 mIU/lt when compared to patients with TSH levels of 0.65 mIU/lt. The authors suggested that this relationship may help the clinicians for FNA indication in cases with upper-normal or high TSH levels (8). Some previous studies also reported that there was no correlation between TSH levels and DTC frequency and poor prognostic factors (9,10,11). One of the largest studies that evaluated the relationship between thyroid cancers and TSH histopathologically was conducted by Kim et al., no correlation was found between TSH and thyroid cancer similarly to our study. In a study by Megan et al. in 2009 (12), a significant relationship was found between TSH and thyroid cancer, but no association was found between aggressive behavior of thyroid cancer and TSH, like our study.

**Table 3. Assocation of TSH with poor prognostic factors in DTC**

| Variables | | n | TSH (mIU/lt) median (min- max) | p value |
|---|---|---|---|---|
| Multifocality | + | 54 | 3.07 (0.01-9.1) | 0.659 |
| | - | 147 | 1.89 (0.01-5.2) | |
| Capsulary invasion | + | 33 | 1.33 (0.01-6.6) | 0.550 |
| | - | 168 | 1.08 (0.01-9) | |
| Vasculary invasion | + | 10 | 1.13 (0.01-9) | 0.565 |
| | - | 191 | 1.21 (0.5-4.5) | |
| Extrathyroidal extension | + | 18 | 1.30 (0.01-9.6) | 0.849 |
| | - | 183 | 1.17 (0.5-4.4) | |
| Lymph node metastasis | + | 36 | 1.05 (0.01-9) | 0.117 |
| | - | 165 | 1.35 (0.01-6.5) | |

More recently, Sohn Y et al. reported no significant associations between serum TSH level and the risk of malignancy in patients with papillary microcarcinomas. However, there was a significant association between serum TSH level and malignancy risk in patients with papillary macrocarcinomas (13). Although there is some convincing evidence to support the relationship between TSH and DTC, on the other hand, there are some data against a role for TSH in the development or progression of thyroid cancers. First, suppression of serum TSH by exogenous thyroid hormone have no significant clinical benefit in patients with low-risk thyroid cancer (14). Second, there is no evidence for a direct oncogenic role of TSH in human thyroid carcinogenesis (15). Third, it was shown that other growth factors such as insulin-like growth factor-I (IGF-I) are more potent in stimulating thyroid cancer growth (16). Fourth, there is an inverse relationship between TSH receptor mRNA levels and aggressive features of cancer (17). Finally, these findings suggest that TSH receptor stimulation via increased levels of TSH may play a role in the growth of benign and malignant thyroid tumors (18,19).

**Limitations and strength**

The strength of our study was that we had a large number of DTC cases (n=201), our patients did not use any medication which could affect thyroid function tests and our examination was based on thyroid surgery instead of FNA. We also have some limitations in this study. Since our study is a retrospective cross-sectional study, the data on preoperative ultrasound imaging and FNA biopsy results were not proper for evaluation, because of missed and non-standardized data.

**Conclusion**

There is growing data about relationship between TSH and thyroid cancer. Despite this growing data, still there is some controversy on this topic. Whether this possible relationship between TSH and thyroid cancers is an actual pathogenetic factor, or a contributing factor to pre-existing tumor progression is still a matter of debate, and a cut-off value for TSH to predict malignancy is unknown. This was the first study to evaluate the relationship between TSH and differentiated thyroid cancer in Turkish population without overt thyroid dysfunction.

**Conflict of Interests**

Authors declare no conflict of interests.

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