

Higher TSH Level is associated with Increased Risk of Malignancy in Thyroid Nodules

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ABSTRACT

Background: To estimate the risk of malignancy of a thyroid nodule, several factors should be taken into account including age, gender, nodule size and history of radiation. Recently, preoperative serum thyroid stimulating hormone levels (TSH) is considered as an independent predictor for thyroid malignancies in patients with diffuse or nodular goiter; higher TSH levels are associated with an increased incidence of thyroid cancer in patients with nodular thyroid disease. We performed a diagnostic accuracy study on serum TSH in patients with malignant and benign thyroid nodules who were referred to the clinics of 5-Aazar and Shahid Sayad Shirazi Hospitals during the years 2014 and 2015.

Methods: Patients with solitary thyroid nodules who were referred to Endocrinology clinics of 5-Aazar and Shahid Sayad Shirazi Hospitals during 2014 and 2015 were enrolled. Patients undergoing medical treatment were excluded. Serum TSH and T4 levels were initially measured in this study, and after performing fine-needle aspiration biopsy of thyroid nodules (FNA), pathology results were compared with TSH serum levels. Demographic information of participants was recorded. Chi-square test

and independent T-test were used for data analysis. The P value ≤ 0.05 was considered statistically significant.

Results: Of 80 patients, 24 (30%) were females with mean \pm SD age of 42 ± 13 years. The mean \pm SD serum TSH level in patients with malignant (N=20) and benign (N=60) nodules were 4.7 ± 2.4 μ U/mL and 2.5 ± 2.3 μ U/mL, respectively. All patients had subclinical thyroid dysfunction. In sensitivity analysis of ELISA, TSH level cut-point in the diagnosis of thyroid malignancies was 3.45 μ U/mL with sensitivity and specificity of 80% and 78%, respectively. Sixteen (80%) of 20 patients in the malignant group had TSH levels above 3.45 μ U/mL. In the benign group, 47 (78.3%) had TSH levels below 3.45 μ U/mL.

Conclusion: We found a significant difference in mean TSH serum level between patients with benign and malignant thyroid nodules; malignancy risk was higher in thyroid nodules from patients with high serum TSH level. The cut point for TSH in the diagnosis of thyroid malignancies is 3.45% with sensitivity of 80% and specificity of 78.3%.

Keywords: Thyroid nodules; TSH; Malignant Thyroid Nodules; Benign Thyroid Nodules; Thyroid Carcinoma

INTRODUCTION

The lifetime risk of developing thyroid nodule ranges between 5 to 10% [1] but the risk of thyroid cancer is much lower; 0.84% and 0.30% in women and men, respectively [2]. Therefore, a clinician needs to differentiate between benign and malignant thyroid nodules. Several clinical

factors are considered when estimating the risk of malignancy in a thyroid nodule, such as age, gender, nodule size, and history of neck radiation. In clinical studies, higher thyroid stimulating hormone (TSH) levels are associated with higher incidence of thyroid cancer in patients with nodular thyroid disease [1-4]. Recently, preoperative serum TSH is considered

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in patients with diffuse or nodular goiter as an independent predictive factor for thyroid malignancies. However, the utility of serum TSH levels in predicting malignant potential of thyroid nodules has not been fully explored and not examined in Iranian patients.

The aim of this study was to investigate serum TSH level in patients with thyroid nodules and determine the cut-off values of TSH to support pre-operative clinical diagnosis of malignancy.

METHODS

This retrospective case-control study was conducted on 20 patients with malignant nodules and 60 patients with benign nodules who were seen at the clinics of 5-Aazar and Shahid Sayad Shirazi Hospitals between 2014 and 2015. Patients were included if they had solitary thyroid nodule and excluded if patients who were actively undergoing medical treatment for thyroid nodules. Of note, all patients had subclinical thyroid dysfunction without overt hypothyroidism and hyperthyroidism. Serum TSH and T4 levels were initially measured in these patients and pathology results were compared with TSH serum levels after performing fine-needle aspiration (FNA) biopsy of thyroid nodules.

Sample size: The sample size was determined with 80% power and error rate of 5%. Considering the standard deviation of 5.5 μ IU/ml and 1.4 μ IU/ml in malignant and benign groups, respectively and difference in means of 3 as well as 3: 1 ratio of benign to malignant groups, 20 patients with malignant nodules and 60 patients with benign nodules were studied.

Ethical Considerations: This study was conducted after obtaining permission from Vice Chancellor for Research and Technology of the university. All interventions in this study were part of the standard treatment process.

Data analysis: The data was entered in SPSS v.16 and the following tests were carried out: data description (mean and standard deviation), data analysis (independent T test) and Mann-Whitney test in case of non-normal data distribution (The significance level was considered less than 0.05).

RESULTS

All 80 patients with solitary thyroid nodules

enrolled in this study had subclinical thyroid dysfunction, 56 (70%) were women, and 20 (25%) had malignant nodules. The mean \pm SD of age was 42 \pm 13 years, youngest patient was 13 years and the oldest patient was 75 years old.

The mean \pm SD of TSH level was 3.05 \pm 2.54 μ IU/ml (men: 3.25 \pm 2.61; women: 2.97 \pm 2.37). We found no relationship between age and serum levels of TSH (correlation = 0.18, P = 0.11).

Using the ROC curve analysis we found that the optimum TSH level cut-point in the diagnosis of thyroid malignancies was 3.45 μ U/mL with sensitivity of 80%, specificity 78%, and area under the curve of 0.79. Based on this cut-off, 16 out of 20 patients (80%) in malignant group and 47 out of 60 patients (78.3%) in the benign group respectively had TSH levels higher and lower than 3.45.

DISCUSSION

In this retrospective case-control study enrolling patients with thyroid nodules, we found that serum TSH levels were higher in patients with malignant nodules than those with benign nodules. We further found that a serum TSH cut-off value of 3.45 μ U/mL had the highest area under the curve with optimum sensitivity and specificity.

The lifetime risk of developing thyroid nodule ranges between 4 to 7% but the risk of thyroid malignancy is much lower. Currently, work-up of a thyroid nodule often involves an invasive test such as FNA biopsy, necessitating the need to discover non-invasive tests that can predict malignancy in thyroid nodules. Epidemiological studies have identified other risk factors. Similar to our study, Boelaert et al. studied 1500 patients without overt thyroid dysfunction who were referred to hospitals in Czech Republic with palpable thyroid enlargement [6]. However, they found a much lower level of TSH to be the predictor of 0.9 μ IU/ml, than our study.

In another study, Zafon et al. evaluated preoperative serum levels of TSH in 386 patients with thyroid nodules diseases. Mean TSH levels in patients with malignant and benign nodules was 2.089 \pm 2.1 9 μ IU/ml and 1369 \pm 1.629 μ IU/ml, respectively [4]. In another study, Kim et al. investigated serum levels of TSH in 1759 patients with differentiated thyroid cancer and a control group [5]. They found that the TSH levels were significantly higher in the thyroid malignancy patients than levels in the control patients (1.95 \pm 0. 9 μ IU/ml vs. 1.62 \pm 0. 9 μ IU/ml,

sP <0.001) and was associated with the risk of thyroid cancer [6]. Similarly, Haymart et al also found that the risk of malignancy was higher in patients with higher serum TSH levels. Further, a higher stage thyroid cancer was associated with higher TSH levels [7].

Despite the consistent association between higher TSH levels and malignant nodules shown in most series, an optimal TSH cutoff value for predicting the risk of cancer has not been characterized. Indeed, the lack of previous studies validating nomograms or equations intended to identify an optimal TSH cutoff value has limited the use of serum TSH levels as a malignancy predictor. Here, we found the TSH cutoff value (≥ 3.45 $\mu\text{U/mL}$) provides the largest area under the curve.

This study has several strengths, as it enrolled patients with thyroid nodules who were evaluated at a single institution and did not exclude patients with abnormal TSH levels; factors that enhance the generalizability of our findings and increases the potential clinical applicability of its data. However, being a case control study, presence of selection bias or information bias cannot be ruled out. Hence, a prospective study will be better able to assess the clinical utility of TSH cut-off value.

CONCLUSION

We found that elevated serum TSH level is associated with higher risk of malignancy and there are significant differences in mean serum levels of TSH in patients with benign and malignant nodules. We also showed that the best cut point for TSH in the diagnosis of thyroid malignancies is 3.45 with sensitivity of 80% and specificity of 78.3%.

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