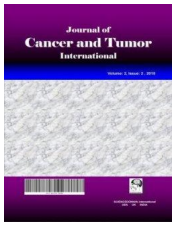

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To Study and Compare the Relationship between Preoperative Serum TSH and Frequency of Differentiated Thyroid Cancer

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Authors' contributions

This work was carried out in collaboration between all authors. Author MFA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors SZH and MPK managed the analyses of the study. Author SV managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Thyroid-stimulating hormone (TSH) plays a key role in the growth and development of thyroid cells and also regulates the function of the thyroid gland. Apart from the multiple risk factors for thyroid cancer like age, male gender, exposure to ionizing radiation and family history of thyroid cancer, higher TSH levels have also been linked to increase the chances of thyroid cancer. This study is performed in a tertiary care hospital over 3 years with 338 samples amongst which 82 patients had DTC and 256 patients had benign thyroid nodules. Serum TSH level was measured by automated enzyme-linked fluorescent assay (ELFA) technique. Biomerieux mini-Vidas hormonal analyzer was used to measure the hormone levels, and the reference ranges were stratified into 4 different groups. Data were analyzed using SPSS 22 version software. Chi-square test was used as a test of significance and p-value of <0.05 was considered as statistically significant. As a conclusion, it can be said that no significant association between higher TSH level and DTC were found. Several authors have investigated the relationship but the results have been inconsistent. A prospective study with a large sample size will be needed for further outcomes.

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1. INTRODUCTION

Thyroid-stimulating hormone (TSH) plays a physiological role in the growth of thyroid cells and also regulates the function of the thyroid gland. Apart from the multiple risk factors for thyroid cancer which include age, male gender, exposure to ionizing radiation and family history of thyroid cancer, higher TSH levels have also been linked to increased frequency of thyroid cancer. High TSH levels have been associated with the pathogenesis of papillary thyroid carcinoma in experiments in mice [1]. TSH interaction with Braf oncogene has been suggested that predisposes thyroid cells to malignant transformation [2]. TSH suppression with suppressive doses of Thyroxine is currently recommended in the postoperative management of DTC.This helps to prevent tumor recurrence. However, studies linking TSH to the risk of thyroid cancer have produced conflicting results. We aimed at evaluating the association between preoperative serum TSH in differentiated thyroid cancer and benign thyroid nodules.

2. MATERIALS AND METHODS

This was a retrospective study conducted in a tertiary care hospital over a period of 3 years. Patients with DTC (on final HPE) and benign thyroid nodules (Solitary/Multinodular goiter) were included in the study. Patients on thyroxine therapy, thyroiditis, Graves Disease and other thyroid malignancies were excluded. Demographic data, TSH, FT3, FT4, USG neck and HPE was recorded. 338 patients were eligible for the study that formed the sample size.82 patients had DTC and 256 patients had benign thyroid nodules.Serum TSH level was measured by automated enzyme-linked fluorescent assay (ELFA) technique. Biomerieux mini-Vidas hormonal analyzer was used to measure the hormone levels using the manufacturer's reagents and calibrators. The normal range of serum TSH is between 0.35 and 5.5 mIU/L. The TSH levels within the normal reference range were stratified into 4 quartile groups for comparison: Group 1) 0.35 to 1.32 mIU/L, Group 2) 1.33 to 2.00 mIU/L, Group 3) 2.01 to 3.22 mIU/L and Group 4) 3.23 to 5.50 mIU/L. Data were analyzed using SPSS 22 version software. Chi-square test was used as a test of significance and p-value of <0.05 was considered as statistically significant.

3. RESULTS

700 patients underwent thyroid surgeries in our institute between 2014 and 2017, of which only 338 patients were eligible for the study that formed the sample size. Among the 338 patients studied, 82 (24.3%) patients were diagnosed with DTC and 256 (75.7%) patients had benign thyroid nodules. Majority of the patients were females in both the benign as well as malignant thyroid diseases with most them being in the age group of 21 to 40 years. (Table 1).

The most common histopathological variant in malignancy was the papillary thyroid carcinoma (PTC) with 64 (78%) patients diagnosed with it. The rest were the micro papillary carcinoma thyroid (12 pts, 14.6%), Follicular variant of PTC (4 pts, 4.9%) and Follicular thyroid carcinoma (2 pts, 2.4%).

With regards to patients with benign thyroid disorders, the majority, 221 patients (86.3%), were diagnosed on histopathology with nodular colloid goiter. The remaining patients were diagnosed with adenomatous hyperplasia (29 pts, 11.3%) and follicular adenoma (6 pts, 2.3%). A comparison of the preoperative serum TSH values was done between benign and malignant thyroid diseases. A higher preoperative serum TSH value of >5.5 was seen in patients with benign thyroid nodules rather than in

Table 1. Demographic data distribution

Demographic data		Benign (%)	Malignant (%)
No of patients (pts)*		256 (75.7)	82 (24.3)
Gender distribution	Female	235 (92)	65 (79)
	Male	21 (8)	17 (21)
Age (in years)	<21	9 (3.5)	6 (7.4)
	21-40	119 (46.4)	33 (41)
	41-60	113 (44.1)	29 (36)
	>60	15 (5.9)	13 (16)

** Percentage in parentheses*

patients with malignant thyroid diseases. This was significant with a p-value < 0.001. Within the normal reference range of TSH (0.35-5.50 mIU/L), which was further subdivided into 4 quartile groups, there was no significant difference in the preoperative TSH values between benign and malignant thyroid diseases in our study. (Table 2)

There was a significant difference in TSH values in female patients between benign and malignant thyroid diseases. A higher percentage of female patients with benign nodules had TSH value of > 5.5. This was significant with a P value <0.05 (Table 3). However in male patients there was no significant difference in TSH between benign nodules and DTC (Table 4).

4. DISCUSSION

In our study the most common thyroid malignancy encountered was papillary carcinoma thyroid. This is consistent with the published literature, where papillary carcinoma thyroid is reported to account for 80% of thyroid malignancies [3]. Papillary carcinoma thyroid is more common in females, and this is similarly reflected in our study.

There are multiple risk factors associated with thyroid malignancy. Risk factors include age male sex, history of radiation and family history of thyroid cancer. The physiological role of TSH on thyroid gland is well known.TSH stimulates the thyrocytes to accumulate iodine and finally produce thyroid hormones.

Several studies have reported on the increased risk of thyroid malignancy associated with higher TSH levels. These studies suggest the possibility that TSH may play a role in the development or progression of thyroid malignancies.

Boelaert K et al [4] in 2006 first reported parallel increases in malignancy risk and serum TSH levels in their prospective study of 1183 patients. They concluded that the increased risk was associated with serum TSH concentrations in the upper half of the normal range. In our study, however, a higher TSH value of >5.5mIU/L was seen more in benign thyroid nodules rather than in thyroid malignancy. This was significant with a p- value < 0.001.

Table 2. Comparison of preoperative serum TSH values between benign versus malignant thyroid

TSH (mIU/L)		HPE number of patients*		P-value
		Benign (%)	Malignant (%)	
Above normal (>5.5)		67 (25.4)	4 (4.9)	< .001
Within normal reference range of 0.35-5.5, TSH divided into 4 Quartile groups.	Group1(0.35-1.32)	52 (28.2)	13 (18.3)	0.16
	Group2(1.33-2.00)	47 (25.5)	17 (23.9)	0.82
	Group3(2.01-3.22)	40 (21.7)	23 (32.4)	0.13
	Group4(3.23-5.50)	45 (24.5)	18 (25.3)	0.90
Below normal (<0.35)		6 (2.3)	6 (7.3)	0.07

** Percentage in parentheses*

Table 3. Comparison of preoperative serum TSH values between benign versus malignant thyroid in female patients

TSH (mIU/L)		HPE - number of female patients*		P-value
		Benign (%)	Malignant (%)	
Below normal (<0.35)		6 (2.6)	5 (7.8)	0.05
Within Normal Reference range of 0.35-5.5, TSH divided into 4 Quartile groups.	Group1(0.35-1.32)	45 (19.1)	7 (10.9)	0.05
	Group2(1.33-2.00)	44 (18.1)	15 (23.4)	0.95
	Group3(2.01-3.22)	36 (15.3)	18 (28.1)	0.16
	Group4(3.23-5.50)	39 (16.6)	15 (23.4)	0.65
Above normal (>5.50)		65 (27.7)	4 (6.3)	< 0.002
Total no of patients		235	64	

** Percentage in parentheses*

Table 4. Comparison of preoperative serum TSH values between benign versus malignant thyroid in male patients

TSH (mIU/L)		HPE- number of male patients*		P-value
		Benign (%)	Malignant (%)	
Below normal (<0.35)		-	1 (5.88)	-
Within normal reference range of 0.35-5.5, TSH divided into 4 Quartile groups.	Group1(0.35-1.32)	7 (33.3)	6 (35.3)	0.81
	Group2(1.33-2.00)	3 (14.3)	1 (5.9)	0.47
	Group3(2.01-3.22)	4 (19)	5 (29.4)	0.44
	Group4(3.23-5.50)	6 (28.6)	3 (17.6)	0.56
Above normal (>5.50)		1 (4.8)	1 (5.88)	-
Total no of patients		21	17	

** Percentage in parentheses*

In a similar study by Jonklaas et al [5] published in 2008, serum TSH levels were compared between 33 patients with benign thyroid disease and 17 patients with thyroid cancer. The mean age of the study group was 45 years as compared to a mean age of 41 years in our study. Jonklaas et al [5] divided the patients further into 4 quartiles groups based on their serum TSH levels. Their study concluded that patients with thyroid cancer had TSH levels in the upper three quartiles of TSH values, compared to patients with benign thyroid diseases. A similar comparison in our study revealed no significant difference in TSH values between benign and malignant nodule among the 4 quartile groups.

Kim K W et al [6] study which comprised of 1080 patients with thyroid cancer and 249 patients with benign thyroid diseases revealed no relationship between TSH level and frequency of PTC. Castro et al [7] similarly did not find a significant relationship between serum TSH and thyroid malignancy. Our present study also had not shown any significant association between higher TSH level and differentiated thyroid cancer.

Huang et al [8] concluded in their study on 741 patients that serum TSH level below the normal reference range was significantly seen in women with papillary carcinoma thyroid than in men. In our study, we observed that female patients with benign nodules had significantly higher TSH values.

All our patients with thyroid malignancy continued to be managed with suppressive doses of thyroxine post thyroidectomy as per ATA [9] (American Thyroid Association) treatment guidelines. However, the possible association between higher preoperative TSH levels and thyroid malignancy could not be established in our study. It is well known that TSH is required by the thyrocytes for their physiological function and for the growth of the gland. It is not surprising that the growth of the remaining malignant transformed thyrocytes is suppressed when suppressive doses of thyroxine is given in postoperative management of differentiated thyroid malignancy. In this context, it is difficult to exclude the importance of TSH in the development of thyroid malignancy. There are multiple genes involved in the development and progression of thyroid cancer which includes Braf, Ras and Ret proto-oncogene. This has been well studied and established. With the ever-increasing knowledge on the genes that are involved in the pathogenesis of thyroid malignancy, we are yet to find a pathway to explain the role of TSH in influencing the genetic factors. Hence till now the American Thyroid Association and the American Association of Clinical Endocrinologists [10] has not recommended strongly on the use of Thyroxine in the preoperative setting to suppress the growth of benign thyroid nodules. Thyroxine suppression leading to a chronic low TSH has deleterious effects on the bone [11] and heart [[12] of the patient leading to increased morbidity and mortality. These risks outweigh its benefits when used in patients with low-risk thyroid malignancy. Tumorogenesis in thyroid cancer is complex highlighting the role of multiple risk factors.In our patients, we could not relate a higher TSH level with thyroid malignancy, but this does not exclude the possible role of TSH in tumor development.

5. CONCLUSION

TSH as a predictor of thyroid malignancy has been evaluated in several studies. The present study did not show a significant association between higher TSH level and DTC. Several authors have investigated the relationship, but

the results have been inconsistent. A prospective study with a large sample size will be needed to evaluate this association further.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Schaller Jr RT, Stevenson JK. Development of carcinoma of the thyroid in iodine-deficient mice. Cancer. 1966; 19:1063–1080.
2. Franco AT, Malaguarnera R, Refetoff S, Liao XH, Lundsmith E,Kimura S, Pritchard C, Marais R, Davies TF, Weinstein LS, Chen M, Rosen N, Ghossein R, Knauf JA, Fagin JA. Thyrotrophin receptor signaling dependence of Braf-induced thyroid tumor initiation in mice. Proc Natl Acad Sci USA. 2011;108:1615–1620.
3. Meza R, Chang JT. Multistage carcinogenesis and the incidence of thyroid cancer in the US by sex, race, stage and histology. BMC public health. 2015;15(1):789.
4. Boelaert K, Horacek J, Holder RL, Watkinson JC, Sheppard MC, Franklyn JA. Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. JClin Endocrinol Metab. 2006;91(11): 4295±301.
5. Jonklaas J, Nsouli-Maktabi H, Soldin SJ. Endogenous thyrotropin and triiodothyronine concentrations in individuals with thyroid cancer. Thyroid. 2008;18(9):943-52.
6. Kim KW, Park YJ, Kim EH, Park SY, Park do J, Ahn SH, Park do J, Jang HC, Cho BY. Elevated risk of papillary thyroid cancer in Korean patients with Hashimoto's thyroiditis. Head Neck. 2011; 33:691–695.
7. Castro MR, Espiritu RP, Bahn RS, Henry MR, Gharib H, Caraballo PJ, Morris JC Predictors of malignancy in patients with cytologically suspicious thyroid nodules. Thyroid. 2011;21:1191–1198.
8. Huang Huang, Jennifer Rusiecki, Nan Zhao, et al. Thyroid-stimulating hormone, thyroid hormones and risk of papillary thyroid cancer. A Nested Case-Control Study, Cancer Epidemiology Biomarkers; 2017.
9. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. The American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer Thyroid. 2016;26(1):1–133.
10. Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedüs L, Paschke R, Valcavi R, Vitti P. Nodules, AACE/ACE/AME task force on thyroid. American association of clinical endocrinologists, American college of endocrinology, and associazione medici endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules-2016 update. Endocr Pract. 2016;22(5): 622–39.
11. Ross DS. Subclinical hyperthyroidism: possible danger of overzealous thyroxine replacement therapy. Mayo Clin Proc. 1988;63(12):1223–9.
12. Heeringa J, Hoogendoorn EH, van der Deure WM, Hofman A, Peeters RP, Hop WC, et al. High-normal thyroid function and risk of atrial fibrillation. The Rotterdam study. Arch Intern Med. 2008;168(20): 2219–24.

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