

Original Research Article**To study and compare the relationship between
preoperative serum TSH and frequency of
differentiated thyroid cancer****Abstract**

Thyroid-stimulating hormone (TSH) plays key role in the growth and development of thyroid cells and also regulates 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 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 was analyzed using SPSS 22 version software. Chi-square test was used as 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 out comes.

Keywords: Thyroid stimulating hormone (TSH), Differentiated thyroid carcinoma (DTC).

INTRODUCTION:

Thyroid-stimulating hormone (TSH) plays a physiological role in the growth of thyroid cells and also regulates 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 in 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.

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 was analyzed using SPSS 22 version software. Chi-square test was used as test of significance and p value of <0.05 was considered as statistically significant.

50 **RESULTS:**

51 700 patients underwent thyroid surgeries in our institute between 2014 and 2017, of which
 52 only 338 patients were eligible for the study that formed the sample size. Among the 338
 53 patients studied, 82 (24.3%) patients were diagnosed with DTC and 256 (75.7%) patients
 54 had benign thyroid nodules. Majority of the patients were females in both the benign as well
 55 as malignant thyroid diseases with most them being in the age group 21 to 40 years. (Table
 56 1)

57 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)

58 * Percentage in parentheses

59 The most common histopathological variant in malignancy was the papillary thyroid
 60 carcinoma (PTC) with 64 (78%) patients diagnosed with it. The rest were the micro papillary

61 carcinoma thyroid (12 pts, 14.6%), Follicular variant of PTC (4 pts, 4.9%) and Follicular
62 thyroid carcinoma (2 pts, 2.4%).

63 With regards to patients with benign thyroid disorders, the majority, 221 patients (86.3%),
64 were diagnosed on histopathology with nodular colloid goiter. The remaining patients were
65 diagnosed with adenomatous hyperplasia (29 pts, 11.3%) and follicular adenoma (6 pts,
66 2.3%). A comparison of the preoperative serum TSH values was done between benign and
67 malignant thyroid diseases. A higher preoperative serum TSH value of >5.5 was seen in
68 patients with benign thyroid nodules rather than in patients with malignant thyroid diseases.
69 This was significant with a p value < 0.001. Within the normal reference range of TSH (0.35-
70 5.50 mIU/L), which was further subdivided into 4 quartile groups, there was no significant
71 difference in the preoperative TSH values between benign and malignant thyroid diseases in
72 our study. (Table 2)

73 Table 2: Comparison of preoperative serum TSH values between benign versus malignant
74 thyroid

TSH (mIU/L)		HPE		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	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

groups.	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

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).

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

DISCUSSION

In our study the most common thyroid malignancy encountered was papillary carcinoma thyroid. This is consistent with published literature, where papillary carcinoma thyroid is

92 reported to account for 80% of thyroid malignancies^[3]. Papillary carcinoma thyroid is more
93 common in females and this is similarly reflected in our study.

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

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

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

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

114 Kim K W et al ^[6] study which comprised of 1080 patients with thyroid cancer and 249
115 patients with benign thyroid diseases revealed no relationship between TSH level and
116 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 (American Thyroid Association) treatment guidelines. However the possible association between higher preoperative TSH levels and thyroid malignancy could not be established in our study.

CONCLUSION

TSH as a predictor of thyroid malignancy has been evaluated in several studies. Present study did not show 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 further evaluate this association.

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