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Association of Thyroid Stimulating Hormone (TSH) with Thyroid Carcinoma (Papillary Carcinoma of Thyroid)

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Abstract | **Original Research Article**

Background*:** Thyroid carcinoma, in most cases, presents clinically as a solitary nodule or as a dominant nodule within a multinodular thyroid gland. Higher serum TSH levels have been found associated with advanced stages of thyroid cancer. ***Objective*:** The aim of the study was Association of Thyroid Stimulating Hormone (TSH) with Thyroid Carcinoma. ***Methods: This cross-sectional study was conducted at the Department of surgery and ENT, Sir Salimullah Medical College and Midford Hospital, Dhaka, Bangladesh from the period of July 2012 to June 2014. A total of 116 patients were included for the study according to following inclusion and exclusion criteria. Other necessary investigations were done if clinically indicated. Statistical analysis of the results was obtained by using window-based computer software devised with Statistical Packages for Social Sciences (SPSS-24). ***Results:*** Out of 116 patients; 30 (25.9%) patients were 15 to 30 years of age, 53 (45.7%) were 31 to 45 years old, 29 (25%) were 46 to 60 years old and only 4 (3.4%) were 61 to 75 years old. The highest patients were belonging to 31 to 45 years age group. The mean age of the patients was 39.5 years. Majority (81.9%) of the patients was female and the rest (18.1%) were male. The most common tumor size was found to be around 2 to 4 cm (28), >4 cm (15) and <2 cm (15) respectively. Majority of the patients 68.1 % were suffering from benign tumor and 12.9% were suffering from malignant tumor. Majority patients with benign and papillary carcinoma had TSH level of 0.1 to 2 mlU/L. ***Conclusion***: Patients with elevated TSH levels are more likely to experience differentiated carcinoma than people with low TSH levels. To generalize these results linking the differences in TSH levels between differentiated thyroid carcinoma and benign thyroid enlargement, multicenter hospital population-based studies are required.

Keywords: Thyroid carcinoma, Growth, Tumor, Thyroid Stimulating Hormone.

INTRODUCTION

Thyroid stimulating hormone (TSH) is essential for the growth and proliferation of differentiated thyroid carcinoma. TSH is a pituitary hormone that promotes thyroid hormone synthesis and growth of thyrocytes. The role of TSH in the initiation or progression of PTC has been well demonstrated. Thyroid cancer is a type of malignant endocrine system tumor with an increasing incidence rate, which consists of four different pathological types: PTC, medullary carcinoma, follicular carcinoma, and undifferentiated carcinoma. Considered a potentially treatable but commonly fatal cancer with increasing incidence due to its slow acting nature and tendency for metastasis, patients often present late for treatment, resulting in poor outcomes. Thyroid-stimulating hormone (TSH) is a growth factor that stimulates thyroid tissue to produce thyroid hormone; also, it affects the growth of thyroid cells and thyroid cancer cells. Thyroid malignancy is common among the endocrine organ and it represents 1% of all malignancy [1]. Incidence ranges from 0.9% to 13% in different part of the world [2]. Thyroid malignancy is classified as primary and secondary. Dunhill classified primary carcinoma into differentiated thyroid cancer (DTC) and undifferentiated: and the DTC again divided into papillary thyroid cancer (PTC) 60%, follicular thyroid cancer (FTC) 20%, Anaplastic carcinoma 10%, Medullary carcinoma 5% Malignant lymphoma 5%. In most cases, thyroid gland harboring

malignancy is clinically indistinguishable from those that do not, and physical examination is therefore deemed largely unhelpful in identifying those patients with thyroid cancer [1]. The challenge to the clinician is to identify the minority of patient with occult thyroid carcinoma who therefore require radical surgical intervention. A major aim of clinical evaluation of patients presenting with thyroid enlargement is to minimize the risk of overlooking thyroid cancer. Recognized clinical parameters raising the suspicious for malignancy include young (<17 yr) or old age (>70 yr), male gender, large (>4 cm) or rapidly growing nodules, and radiation exposure history. Any thyroid swelling usually first diagnosed by some baseline investigation like ultrasonography (USG), Fine needle aspiration cytology (FNAC) and thyroid function test.

Fine needle aspiration cytology (FNAC) is a primary method for detecting malignant nodules; 10%-25% of thyroid nodules are categorized as indeterminate nodules. Classification for indeterminate nodules is defined as "atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS)" and "follicular neoplasm (FN) or suspicious for follicular neoplasm (SFN)" under the Bethesda classification system and the risk of malignancy of the FN/SFN category nodules is approximately 15% to 30%. This association is more frequent for PTC than other DTC or benign thyroid conditions [5]. The mechanism(s) responsible for association is currently unclear but may be multi-factorial because Hashimotos thyroiditis (HT) and PTC share a number of morphological, immune-histochemical, and molecular features. These are RET/PTC gene [6], association of P^{63} proteins etc [7].

Numerous studies were performed in order to differentiate benign and malignant thyroid nodules using clinical factors other than cytology. Unfortunately, there are currently no useful differentiating markers except for some well-known risk factors such as positive family history, tumour size and age mention earlier. The gold standard method for preoperative diagnosis of malignancy is FNAC [1]. In many cases FNAC cannot differentiate micro-nodules (tumor<1 c.m.) and follicular carcinoma from benign which are usually confirmed histopathologically (postoperatively) and thus requiring further revision surgery. In our study, I will try to elucidate the role of TSHs as a predictive marker that could distinguish benign and malignant thyroid nodules and any other occult malignancy. On the other hand, if we can establish the role of TSH in the diagnosis of thyroid malignancy, then we can do the suspected cases one step ahead surgery (in case of inconclusive FNAC) and able to give the patient better management.

OBJECTIVE

The aim of the study was Association of Thyroid Stimulating Hormone (TSH) with Thyroid Carcinoma.

METHODS

This cross-sectional study was conducted at the Department of surgery and ENT, Sir Salimullah Medical College and Midford Hospital, Dhaka, Bangladesh from the period of July 2012 to June 2014. A total of 116 patients were included for the study according to following inclusion and exclusion criteria. All the patients admitted in different units of Otorhinolaryngology ward with thyroid enlargement who underwent thyroidectomies were included in this study. Inclusion Criteria were Age above 10 years and patients presenting with thyroid swelling. Exclusion Criteria were Patients presented with recurrent thyroid swelling, Patients who were diagnosed case of Hashimoto's thyroiditis and Graves' disease and Patients presented with other autoimmune diseases. Other necessary investigations were done if clinically indicated. Statistical analysis of the results was obtained by using window-based computer software devised with Statistical Packages for Social Sciences (SPSS-24). The present study was conducted after receiving approval from the Medical and Health Research Ethics Committee (MHREC).

RESULTS

The total study population was 116 aged 15-75 years. In Table-1 shows age distribution of the patients where most of the patients 53(45.7%) belongs to 31 to 45 years age group. The Figure-1 shows of FNAC test result 79(68.1%) had Benign, 5(4.3%) had Follicular neoplasm, 15(12.9%) had Malignant, 2(1.7%) had Metastatic, 1(0.9%) had Nodular, 2(1.7%) had Nodular follicular, 9(7.8%) had Nodular follicular and 3(2.6%) had Suspicious. The Table shows the diagnostic values (SEN, SPE, PPV, NPV) of TSH, FNAC and combination of FNAC & TSH & autoantibodies By ROC the area of TSH under the curve were at Table shows the diagnostic value of Thyroid Stimulating Hormone (TSH). It shows the highest PPV of TSH was 46% at 20^{th} percentile at different cut of values were calculated. Table shows that the highest PPV is 96% for FNAC.

Table-1: Demonstrate and distribution of the study according to age.

Age Distribution	n=116	%
15 to 30 years	30	25.9
31 to 45 years	53	45.7
46 to 60 years	29	25.0
61 to 75 years	4	3.4
Total	116	100.0

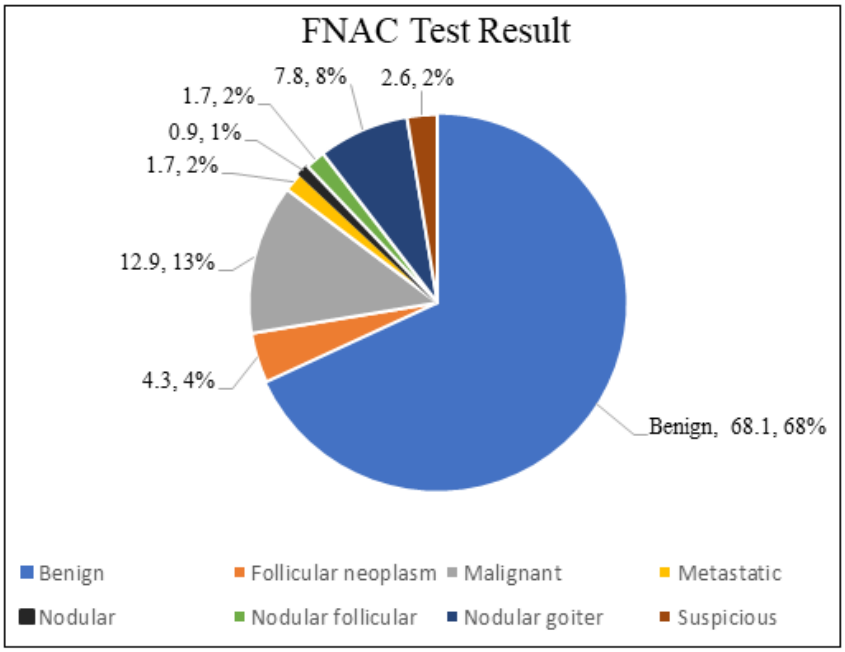

Figure-1: Demonstrate pie chart of the study according to FNAC Test Result

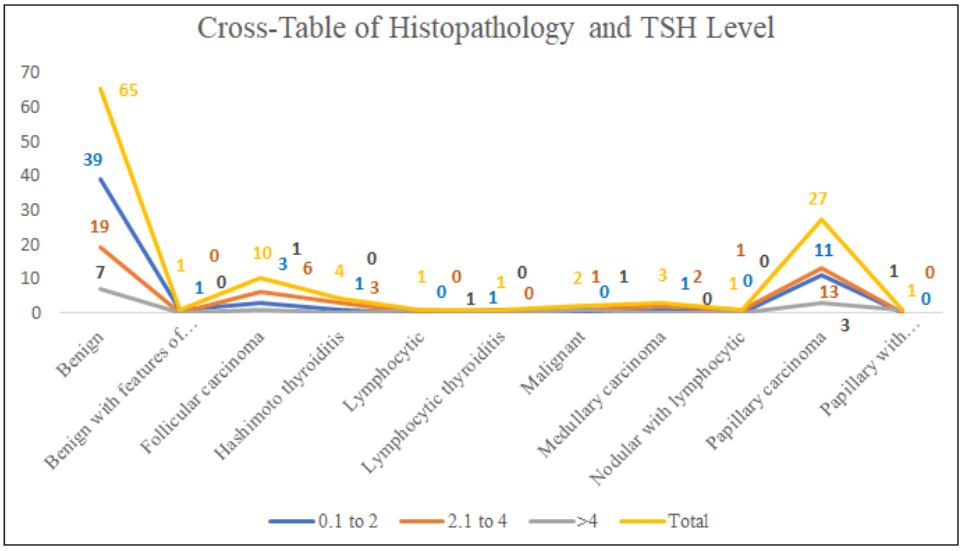

Figure-2: Demonstrate line chart of the study according to Cross-Table of Histopathology and TSH Level

Table-2: Demonstrate and distribution of study population (Benign and Malignant) of TSH level

TSH (mlU/L)	Benign (n)	Malignant (n)
0.1 to 1	19	3
1.0 to 2	20	2
2.1 to 3	18	3
3.1 to 4	7	3
>4	10	3

Table-3: The performance of diagnostic test at optimum cut-off value of TSH, FNAC, FNAC+TSH, FNAC+TPO-Ab, FNAC+Tg-Ab, FNAC+TgAb+ with Papillary Carcinoma of Thyroid

Variables	ROC Area Under the Curve	Cut off Point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
TSH	0.12	4.2	84.7	88.9	15.3	91.9
FNAC			50	98	96	72
FNAC+TSH			94.1	8.5	15.7	88.9

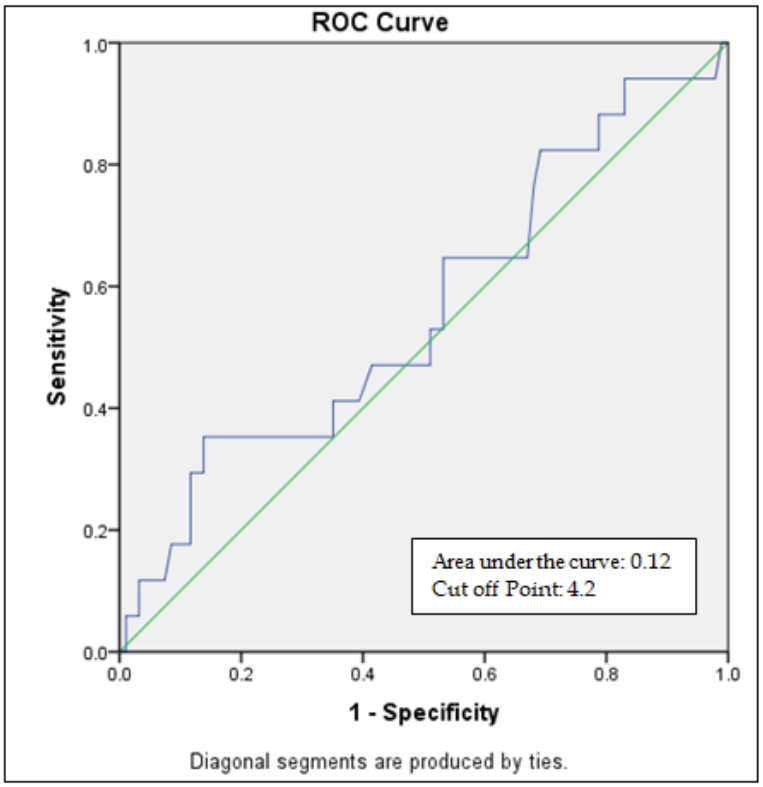

Figure-3: The receiver operator characteristics (ROC) curve of various cut-off points of TSH during FNAC to detect papillary carcinoma, Area under the ROC curve is 0.12

Table-4: The optimum cut-off value of histopathology test for diagnostic thyroid swelling by TSH

Variables	Percentile	Cutoff Point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
TSH	10th	0.520	59	52	27	79
	20th	0.794	38	85	46	80
	25th	1.090	45	74	37	80
	30th	1.360	34	70	27	75
	40th	1.572	20	80	26	80
	50th	2.030	57	43	26	74
	60th	2.310	59	52	27	79
	70th	2.582	53	64	22	79
	75th	2.980	75	80	25	81
	89th	3.458	80.1	85.3	20	85
	90th	4.480	84.7	88.9	15.3	91.9

DISCUSSION

This cross-sectional study was done in the department of General Surgery and Otolaryngology & Head-Neck surgery, Sir Salimullah Medical College Mitford Hospital and BSMMU, Dhaka Medical College, Bangladesh Medical College and Anower Khan Mordern Medical College of Dhaka City from July 2012 to June 2014. For this study, 116 patients of thyroid swelling were studied by detailed history, clinical examination, thyroid hormone assay, ultrasonogram, thyroid scan, FNAC, Thyroid Auto Anti bodies (TgAb and TPO) and histopathological examinations.

C.A Spencer et.al mentioned the prevalence of circulating thyroid auto-antibodies were increased nearly 3 folds in patient with differentiated thyroid carcinoma (DTC) compared with general population [9]. Unger P. et al also mentioned that the occurrence of thyroid auto-antibodies (TPO-Ab & Tg-Ab) in the circulation varies from 10 to 25% in adult population depending on age & gender and the highest prevalence occurring in post-menopausal woman [10]. In this series Fine needle Aspiration Cytology (FNAC) was done in all 116 patients and were grouped into, benign (89), malignant (17), follicular neoplasia (7) and suspicious for malignant (3) group. These FNAC outcomes were compared with thyroid auto-antibodies and histopathological reports.

And of 28 raised ATA 27 (96.4%) were malignant and 1(3.6%) were benign predictive value of malignant group for ATA within normal limits raised ATA were 81.8% and 96.4% respectively. Ahmed T also had the similar findings and, in his study, predictive values were 81.25% and 92.85% respectively [11]. In similar study was done by Wong SL. Et al. with 960 patients who underwent thyroidectomy [12]. He had founded that of 960 patients, 784 had preoperative FNAC of thyroid nodules. Final histology showed 758 benign and 202 malignant cases. Overall thyroid antibodies were not found to be a predictor of thyroid carcinoma in his study (p=0.161) (two-sided probability). But in his study, he also found that with benign FNAC, positive thyroid antibodies (raised serum thyroid antibodies) increased the risk of thyroid malignancy (odds ratio2.16; 95% confidence interval 1.11 to 4.21, P = 0.027). Yalcin S et al., also found thyroid autoantibody was determined in 32/135 patients (23.7%) with thyroid cancer, and 90/435 patients (20.6%) with benign lesions and this difference was not significant [13].

Patients with HT, Graves's disease, and thyroid nodules with higher TSH levels had a higher frequency of PTC, as did patients with HT, Graves' disease, and thyroid nodules with higher TSH levels. There was a connection between a higher serum TSH level and a higher risk of thyroid cancer [14]. In this study, the most common tumor size was found to be around 2 to 4 cm (28), >4 cm (15) and <2 cm (15) respectively. Consistency of most tumor was firm. Previous research has found that serum TSH levels in large benign thyroid nodules are linked to the prevalence of papillary thyroid cancer, and that preoperative serum TSH levels are higher in patients with more advanced tumors and larger tumors [15]. In this study, majority of the patients 68.1% were suffering from benign tumor and 12.9% were suffering from malignant tumor. Fiore et al published a report that established the correlation between TSH and thyroid cancer and addressed recent findings in the field which included subjects diagnosed on cytology in a large series of patients submitted to fine needle aspiration biopsy of thyroid nodules, after validating cytology in a series of 3,406 nodules from 3,004 patients who underwent surgery [16]. The link between serum TSH levels and the risk of papillary thyroid cancer (PTC) was investigated further in 10,178 patients with nodular goiter and a cytological diagnosis of PTC (n = 497) or benign nodular thyroid disease (n = 9,681). Serum TSH was significantly higher in PTC than in patients with benign nodular thyroid disease. The frequency of PTC was directly correlated to serum TSH levels, being the lowest in patients with subnormal TSH values and the highest in patients with TSH values between 1.6 and 3.4 mIU/L.

In this study we found out of 116 patients, 27 (23.3%) patients were diagnosed with PTC and only 3.4% of the patients were diagnosed with Hashimoto thyroiditis. It shows the highest PPV of TSH was 46% at 20th percentile at different cut of values were calculated. Table shows that the highest PPV is 96% for FNAC. Patients with high TSH levels have a higher risk of developing malignant tumors (differentiated thyroid carcinoma) than patients with low TSH levels. Malignant nodules were observed to be substantially more prominent in males, had more compression effects, were more likely to be palpable and correlated with lymphopathy, and were linked to higher TSH levels, according to another report [17]. TSH suppressive therapy has been commonly used to prevent disease progression in patients with DTC, especially in patients with advanced and metastatic DTC, based on these findings [18].

Limitation of the Study

This was a cross-sectional study with a small sized sample. So, the findings of this study may not reflect the exact scenario of the whole country.

CONCLUSION

In this study TSH were raised in both benign and malignant conditions. Patients with elevated TSH levels are more likely to experience differentiated carcinoma than people with low TSH levels. Thyroid auto-antibodies could not predict the malignant condition of thyroid in this study. FNAC is statistically significant to detect malignant condition of thyroid pre-operatively.

RECOMMENDATION

Studies with larger numbers of patients, with more homogenous patient populations, and better correlation between the onset of symptoms and blood Sampling and more similarity in the assay techniques are required in order to resolve the issue.

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