IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 19, Issue 9 Ser.8 (September. 2020), PP 59-65
www.iosrjournals.org

Higher Serum Thyroid Stimulating Hormone (TSH) Concentration in Thyroid Nodule Patients is Associated with Risk of Differentiated Thyroid Carcinoma

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Abstract
Background:*Serum thyroid stimulating hormone (TSH) is a well-established growth factor for thyroid nodules. And suppression of TSH concentrations byproviding exogenous thyroxine may impede with the growth of established nodules as well as the formation of new thyroid nodules.* ***Objective:****The main objective of the study was to assess association between the serum TSH concentration and differentiated thyroid carcinoma.* ***Materials and Methods:****This cross sectional study was conducted in the Department of Otolaryngology-Head & Neck Surgery of Bangabandhu Sheikh Mujib Medical University, Dhaka from January 2014 to June 2015. Total number of patients were 228, among them 69 were as case of differentiated thyroid carcinoma (DTC) group and 159 as control of benign thyroid nodule (BTN) group. The thyroid gland was assessed by palpation in all patients. Estimation of serum TSH concentrations were performed by automated immune chemiluminescent assay. Detailed history and clinical examination was done. Data were compiled and analyses were done by SPSS version 22.0.* ***Results:****In this study 34.8% patients belonged to age <30 years in DTC group, 19(11.9%) in BTN group. 78.3% patients were female in DTC, 132(83.0%) in BTN group. 52.2% patients had solitary thyroid nodule in DTC, 66(41.5%) in BTN group. 55.1% patients were found TSH level 1.71-5.50 µIU/mL in DTC, 29(18.2%) in BTN group. Mean TSH level was 1.25±1.09 µIU/mL in DTC group and 2.79±2.45 µIU/mL in BTN group. Bivariate logistic regression analysis shows serum TSH concentration 1.71-5.50µIU/mL were around 7 times higher risk of developing DTC compared to serum TSH concentration <0.35 µIU/mL. This association was statistically significant (OR=6.724, 95% CI 1.779-25.411, P=0.005), however, gender, age group and number of nodule were not statistically significant. After mutual adjustment, serum TSH concentration 1.71-5.50 µIU/mL were around 8 times higher risk of developing differentiated thyroid carcinoma compared to serum TSH concentration <0.35 µIU/mL. This association was statistically significant (AOR=7.891, 95% CI 1.712-36.376, P=0.008). In addition, serum TSH concentration ≥5.51 µIU/mL were around 14 times higher risk of developing differentiated thyroid carcinoma compared to serum TSH concentration <0.35 µIU/mL which was statistically significant (AOR=13.861, 95% CI 1.503-127.790, P=0.020). Sensitivity of FNAC was 86.96%, specificity was 96.2%, PPV was 90.90% and NPV was 94.44%. Sensitivity of TSH was 60.87%, specificity was 79.87%, PPV was 56.76% and NPV was 82.47%.* ***Conclusion:****The risk of DTC in thyroid nodules increases in parallel with serum TSH concentrations even within the normal range. TSH concentration at presentation is an independent predictor of differentiated thyroid carcinoma.*

Key words: *Thyroid stimulating hormone (TSH), fine-needle aspiration cytology (FNAC), thyroid nodule, differentiated thyroid carcinoma (DTC), goitre, benign thyroid nodule (BTN).*

Date of Submission: 10-09-2020 Date of Acceptance: 25-09-2020

I. Introduction

Thyroid nodules are very common, with an estimated prevalence of 4–7% by palpation.[1] Clinically apparent thyroid nodule were present in 6.4% of women and 1.6% of men with an estimated annual incidence, by palpation, of 1: 1,000.[2] The annual incidence of thyroid carcinoma is 1–2 per 100,000 populations, which accounts for 90% of all endocrine malignancies, 1% of all human malignancies and 0.5% of all deaths from malignancies(Landis et al. 1998).[3] Therefore, thyroid nodules constitute a diagnostic challenge, mainly because of the need to exclude thyroid malignancy, avoiding unnecessary thyroid surgery in patients with benign nodules.Risk factors of thyroid malignancy are patient's age under 30 or over 60 years, male sex (8% vs. 4% in female), nodule size >4 cm, rapidly growing nodules (especially during suppressive thyroxine therapy), history of head and neck irradiation and family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia (MEN2).[4-5]Thyroid carcinoma, in most cases, presents clinically as a solitary nodule or as a dominant nodule within a multinodular thyroid gland.[5]Nevertheless, only 5–15% of the clinically apparent thyroid nodules are malignant.[6] Prediction of malignant potential of thyroid nodule was first evaluated with TSH as biochemical marker. An elevated TSH is associated with an increased risk of malignancy.[7]The majority of patients with Benign or malignant thyroid nodule(s) are euthyroid. However, serum TSH measurement is recommended at presentation in all patients with a thyroid nodule.[8-9]Recently, Boelaert et al.[10] have proposed TSH at presentation as a novel predictor of malignancy in patients with thyroid nodules. All their patients were euthyroid, but some had subclinical hyperthyroidism or subclinical hypothyroidism. The prevalence of malignancy increased with TSH concentration at presentation, even within the normal range of TSH.Serum TSH is a well-established growth factor for thyroid nodules and suppression of serum TSH concentrations by administering exogenous thyroxine may interfere with the growth of established nodles as well as the formation of new thyroid nodules. Additionally, differentiated thyroid carcinomas express the TSH-receptor on their cell membranes. TSH has a trophic effect on thyroid carcinoma growth, which is likely to be mediated by TSH receptors. Animal data demonstrated that TSH suppression in rats exposed to radioiodine prevents the formation of thyroid cancer. However, there are no data in humans that suggest a protective effect of TSH suppression on oncogeesis.[11] Nevertheless, thyroxinetherapy for TSH suppression after thyroidectomy for differentiated thyroid carcinomas is independently associated with reduced recurrence and mortality. This trophic effect of TSH on thyroid tissue that promotes neoplasia and carcinogenesis could be a possible explanation for the increased risk associated with serum TSH concentrations in the upper tertile of the normal range.[12]This study was aimed to investigate whether serum TSH at presentation is a predictor of differentiated thyroid carcinoma in patients with thyroid nodules.Looking into the potentiality of TSH as biochemical marker would provide surgeons better opportunity to predict malignant potentiality of thyroid nodule and to make decision for management planning.

II. Materials And Methods:

This cross sectional study was conducted in the Department of Otolaryngology-Head & Neck Surgery of Bangabandhu Sheikh Mujib Medical University, Dhaka from January 2014 to June 2015. Within the study period collected number of DTC was 69(case), while Benign thyroid nodule was 159(control), total number of patients was 228. Presentation with a solitary thyroid nodule or at least one dominant thyroid nodule within a multinodular goiter, detected by clinical examination and USG of thyroid, thyroid nodules diagnosed by FNAC, either benign or malignant (differentiated thyroid carcinoma, serum concentrations of thyroid stimulating hormone (TSH) and free thyroxine(FT4) recorded before any medical intervention, including thyroxine suppression therapy, serum concentration of FT4 was within normal range were included in this study. Diffuse goiter, hyperthyroid,hypothyroid, patients who were treated for any thyroid disorder were excluded from the study. The thyroid gland was assessed by palpation in all patients. Detailed history and clinical examination was done to determine any obvious clinical feature of malignancy and any feature of thyroid dysfunction. All the data were recorded in a structured questionnaire. The thyroid nodules were first confirmed with ultrasonography at the department of Radiology and Imaging, BSMMU. The serum FT_4 and TSH concentrations were measured by automated immunochemiluminescent assay (ICMA) (Immulite, California, USA) at the department of Microbiology and Immunology, BSMMU. FNAC was done in the department of Pathology, BSMMU. After surgery a final histological result was attempted in every case by histopathology, which was taken as the gold standard. All the patients of DTC, revealed by histopathology report were considered as cases. And all the patients of benign thyroid noduleswere considered as control group.According to serum TSH concentration, all patients were classified into five groups: subclinical hyperthyroidism[TSH<0.35(group 1)], subclinical

hypothyroidism [TSH≥5.51 (group 5)], whereas those with TSH concentration within the normal range were subdivided into three tertiles of similar size [TSH 0.35–0.90 µIU/mL (group 2); TSH 0.91–1.70 µIU/mL (group 3); TSH 1.71–5.50 µIU/mL (group 4)]. Collected data were compiled and appropriate analyses were done by using computer based software, SPSS version 22.0. The mean values were calculated for continuous variables. The quantitative observations were indicated by frequencies and percentages.Multivariate logistic regression analysis (adjusted) was used to evaluate the independent influence of factors including sex, nodule type (solitary or dominant), age and serum TSH concentration at presentation on the final diagnostic outcome. Age and TSH was used as categorical variables in this analysis. A P value less than 0.05 was considered to be statistically significant.

III. Results:

In this study, a total of 228 patients were included as study population, they were divided into two groups 69 cases as DTC and another 159 cases benign thyroid nodule as control. More than one third (34.8%) patients belonged to age <30 years in DTC group 19(11.9%) in BTN group. More than three fourth (78.3%) patients were female in DTC group 132(83.0%) in BTN group. More than half (52.2%) patients had solitary thyroid nodule in DTC group 66(41.5%) in BTN group. Age was statistically significant (p<0.05) between two group (Table-I). Majority (55.1%) patients were found TSH level 1.71-5.50 µIU/mL in DTC group 29(18.2%) in BTN group. Mean TSH level was 1.25±1.09 µIU/mL in DTC group and 2.79±2.45 µIU/mL in BTN group. The difference was not statistically significant (p>0.05) between two group (Table-2). Bivariate logistic regression (unadjusted) analysis shows among thyroid nodule patients male were less likely to have DTC compared to female. However, this association was not statistically significant (OR=0.73, 95% CI 0.36-1.49, P=0.396). This also reveals younger age (<30) were more likely to have DTC compared to old age (≥70) which was not statistically significant (OR=1.14, 95% CI 0.20-6.28, P=0.878). Again solitary thyroid nodule had higher risk to be DTC than multinodular goiter, but the difference was not significant statistically (OR=1.29, 95% CI 0.73-2.27, P=0.377). The analysis shows serum TSH concentration 1.71-5.50µIU/mL were around 7 times higher risk of developing DTC compared to serum TSH concentration <0.35 µIU/mLThis association was statistically significant (OR=6.724, 95% CI 1.779-25.411, P=0.005) (Table-3). Multivariate logistic regression (adjusted) analysis shows among thyroid nodule patients male were more likely to have DTC compared to female. However, this association was not statistically significant (AOR=1.745, 95% CI 0.692-4.399, P=0.238). This also reveals younger age (<30) were less likely to have DTC compared to old age (≥70) which was not statistically significant (AOR=0.96, 95% CI 0.16-5.64, P=0.968). Again solitary thyroid nodule had higher risk to be DTC than multinodular goiter, but the difference was not significant statistically (AOR=1.13, 95% CI 0.71-1.83, P=0.151). Multivariate regression analysis (adjusted) shows increased serum concentration of TSH developing higher risk of differentiated thyroid carcinoma. After mutual adjustment (gender, age, number of nodules) serum TSH concentration 1.71-5.50 µIU/mL were around 8 times higher risk of developing differentiated thyroid carcinoma compared to serum TSH concentration <0.35 µIU/mL. This association was statistically significant (AOR=7.891, 95% CI 1.712-36.376, P=0.008). In addition, serum TSH concentration ≥5.51 µIU/mL were around 14 times higher risk of developing differentiated thyroid carcinoma compared to serum TSH concentration <0.35 µIU/mL which was statistically significant (AOR=13.861, 95% CI 1.503-127.790, P=0.020) (Table-4). Sensitivity of FNAC was 86.96%, specificity was 96.2%, PPV was 90.90% and NPV was 94.44%. Sensitivity of TSH was 60.87%, specificity was 79.87%, PPV was 56.76% and NPV was 82.47% (Figure-III).

Table 1: Demographic characteristics of the study patients (n=228)

Demographic characteristics	DTC (n=69)		BTN (n=159)		P-value
	n	%	n	%	
Age (years)					
<30	24	34.8	19	11.9	
30-39	21	30.4	39	24.5	
40-49	9	13.1	51	32.1	0.001[s]
50-59	12	17.4	33	20.8	
60-69	0	0.0	11	6.9	
≥70	3	4.3	6	3.8	
Gender					
Male	15	21.7	27	17.0	0.395[ns]
Female	54	78.3	132	83.0	
Nodules detected by USG					
Solitary	36	52.2	66	41.5	0.377[ns]
Multiple	33	47.8	93	58.5	

P value reached from Chi-square test

BTN= Benign Thyroid nodule
DTC= Differentiated Thyroid Carcinoma

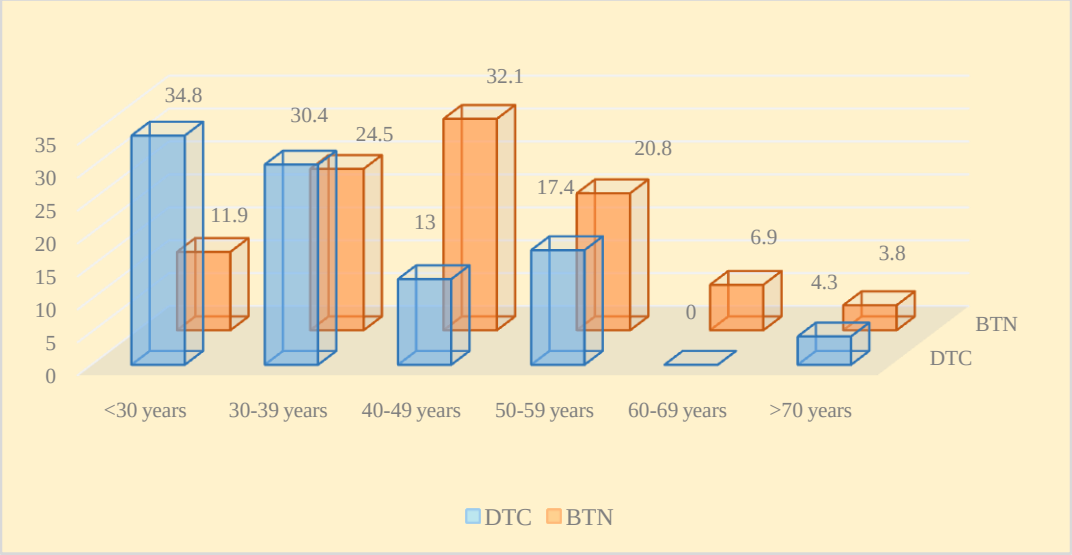

Figure 1: *Patients Age Wise Distribution of DTC & BTN groups*

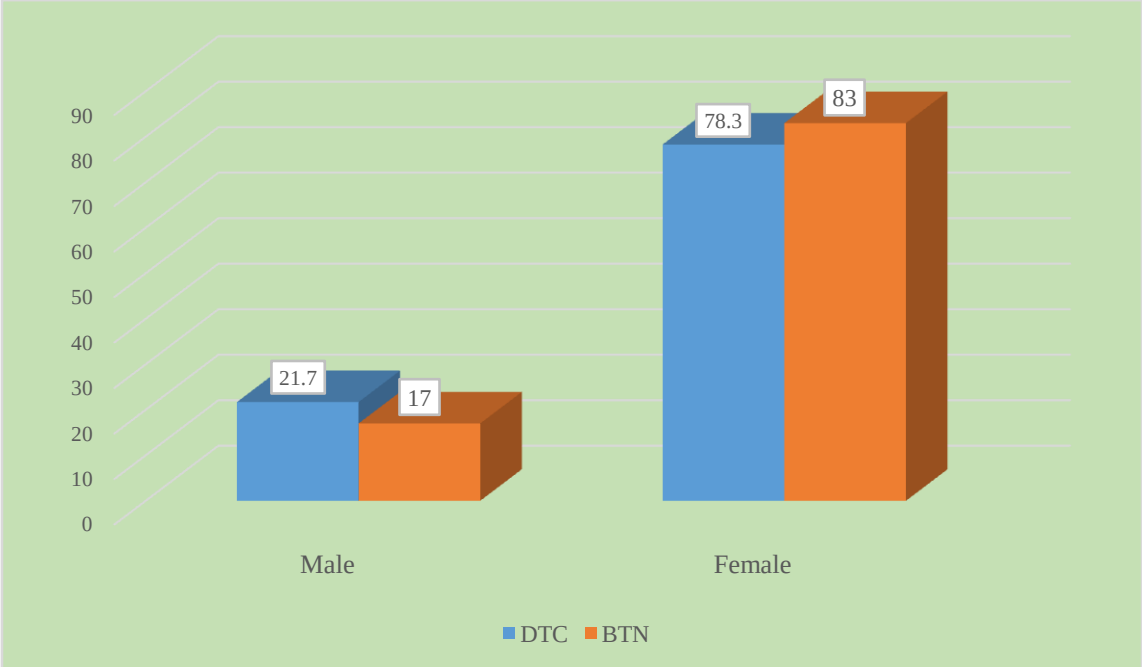

Figure I1: *Patients Sex Wise Distribution of DTC & BTN groups*

Table 2: TSH level of the study patients (n=228)

TSH (µIU/mL)	DTC (n= 69)		BTN (n= 159)		P-value
	n	%	n	%	
<0.35	4	5.8	16	10.1	
0.35-0.90	3	4.3	65	40.9	
0.91-1.70	21	30.4	47	29.6	
1.71-5.50	38	55.1	29	18.2	
>5.50	3	4.3	2	1.3	
Mean±SD	1.25±1.09		2.79±2.45		0.001[$]

Independent t-test was done to measure the level of significance

Table 3: Bivariate logistic regression (unadjusted) among benign thyroid nodules and differentiated thyroid carcinoma with selected demographics and other characteristics

Variables	ORs	95% CI	P-value
Gender			
Male	0.73	0.36-1.49	0.396
Female	1		
Age group (year)			
<30	1.14	0.20-6.28	0.878
30-39	0.53	0.10-2.90	0.472
40-49	0.17	0.03-1.01	0.052
50-59	0.36	0.06-2.05	0.252
60-69	0.00	0.00	0.999
≥70	1		
No. of nodules			
Solitary	1.29	0.73-2.27	0.377
Multiple	1		
Serum TSH (µIU/mL)			
<0.35	1		
0.35-0.90	0.231	0.042-1.258	0.090
0.91-1.70	2.234	0.584-8.550	0.240
1.71-5.50	6.724	1.779-25.411	0.005
≥5.51	5.00	0.660-37.852	0.119

Table 4: Multivariate logistic regression (adjusted) among benign thyroid nodules and differentiated thyroid carcinoma with selected demographics and other characteristics

Variables	AORs	95% CI	P value
Gender			
Male	1.745	0.692-4.399	0.238
Female	1		
Age group (year)			
<30	0.96	0.16-5.64	0.968
30-39	0.57	0.10-3.25	0.534
40-49	0.10	0.01-.70	0.020
50-59	0.19	0.03-1.25	0.085
60-69	0.00	0.00	0.998
≥70	1		
No. of nodules			
Solitary	1.13	0.71-1.83	0.151
Multiple	1		
Serum TSH (µIU/mL)			
<0.35	1		
0.35-0.90	0.195	0.032-1.190	0.077
0.91-1.70	3.391	0.740-5.538	0.116
1.71-5.50	7.891	1.712-6.376	0.008
≥5.51	13.861	1.503-127.790	0.020

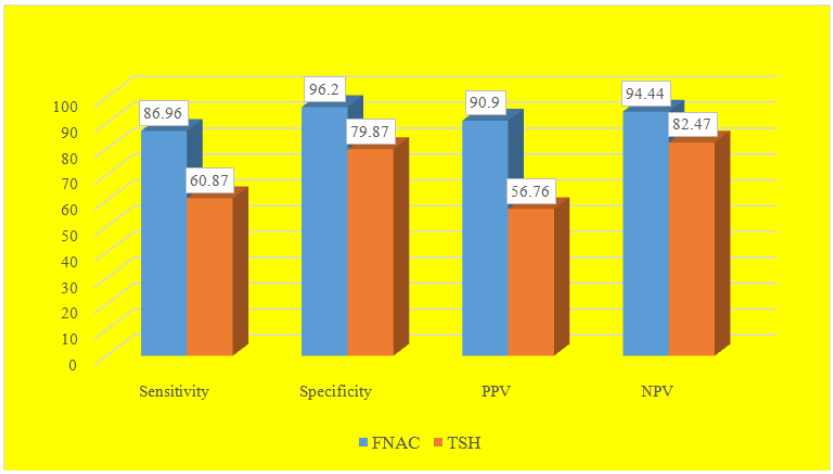

Figure 1II: *Sensitivity, Specificity, PPV, and NPV of FNAC and TSH compared to histopathology.*

IV. Discussion:

Thyroid enlargement is a common clinical problem. Most patients with thyroid enlargement can be managed conservatively after malignancy is ruled out. The challenge to the clinician being to identify the minority of patients with thyroid cancer who therefore require surgical intervention. Thyroid cancer is the most common endocrine malignancy and its incidence continues to rise. Thyroid carcinoma in most cases, presents clinically as a solitary nodule or as a dominant nodule within a multinodular thyroid gland. More recently, a number of studies have suggested that higher concentrations of TSH, even within the normal range are associated with a subsequent diagnosis of thyroid cancer in patients presenting with thyroid nodules.[13]In this study it was observed that More than one third (34.8%) patients belonged to age <30 years in DTC group 19(11.9%) in BTN group. Age was statistically significant (p<0.05) between two group. More than three fourth (78.3%) patients were female in DTC group 132(83.0%) in BTN group. More than half (52.2%) patients had solitary thyroid nodule in DTC group 66(41.5%) in BTN group. Jonklaaset al.[14] in their study observed that highest incidence of thyroid cancer was seen in the age group less than 30 years (32%). Similar observation was made in the study were in majority of subjects were in the age group 26-40 years (44%).This suggests that thyroid malignancies are common in younger and middle age group and common among females than males. In the study by Boelaertet al.[10]the highest incidence of thyroid malignancy was seen in patients presenting with a solitary nodule (n = 861, 10.8%), compared with those who presented with a diffuse or nodular goitre (n = 639, 4.2 %,). In the present study majority of subjects with solitary thyroid nodule (n= 100, 83.3%) had malignancy, compared to multinodulargoitre (n = 20, 16. 7%).In this study it was observed that majority (55.1) patients were found TSH level 1.71-5.50 µIU/mL in DTC group 29(18.2%) in BTN group. Mean TSH level was 1.25±1.09 µIU/mL in DTC group and 2.79±2.45 µIU/mL in BTN group. The difference was not statistically significant (p>0.05) between two group, which is in accordance with published data.[15]The difference was statistically significant (P<0.001). Although both of them falls within the normal range, the higher mean TSH in DTC compared to benign thyroid nodule suggested that TSH was involved in the pathogenesis of DTC. A TSH level above the population mean had an increased risk of developing DTC relative to a TSH level below the mean.Further analysis indicated significantly increased odds ratios for the presence of differentiated thyroid carcinoma in patients with TSH greater than 1.71 µIU/mL (AOR-7.891, 95% CI 1.712-36.376, P=0.008) after adjustment for patients' gender, age, and goiter type. It is well documented that TSH has a trophic effect on thyroid cancer growth, which is most likely mediated by TSH receptors on tumor cells,[16] and furthermore that TSH suppression is an independent predictor of relapse-free survival from differentiated thyroid cancer.[17] We proposed that, the risk increase associated with serum TSH concentrations in the upper tertile of the normal range, and even more strikingly in those whose TSH measurements were above normal (AOR-13.861,95% CI 1.503-127.790, P=0.020), may at least in part be mediated by this trophic effect of TSH. An increased risk of underlying malignancy in men, compared with women, has been demonstrated previously.[1,18]Although a few smaller studies indicated patients' gender not to be helpful in predicting risk of carcinoma.[19,20]More recently, a retrospective case series of 1009 patients evaluating the natural history of cytologically benign thyroid nodules using ultrasonography indicated that patient's gender did not predict nodule growth.[21] In this series, multivariate logistic regression analysis (adjusted) identified that among thyroid nodule patients male were more likely to have differentiated thyroid carcinoma comparedto female. However, this association was not statistically significant (AOR=1.745, 95% CI 0.692-4.399, P=0.238). In this study patients presenting with a solitary nodule on USG at presentation had higher risk of developing DTC when compared with those presenting with a multinodular goiter, but the difference was not significant statistically (AOR=1.13, 95% CI 0.71-1.83, P=0.151). This finding is in accordance with published data.[22] However, controversy still exists over that matter.[6] The use of USG is advantageous in this study, as USG is more accurate than palpation in differentiating solitary nodules from dominant nodules and it approaches the frequency of thyroid nodules found in autopsy studies.[23,24]Furthermore, almost 50% of the patients referred for a palpable solitary nodule were found to have multiple nodules on USG.[25]We observed higher rates of malignancy in ages under 30 years in this study, as reported elsewhere.[26,27]After adjustment in multivariate logistic regression analysis younger age group (<30 years) were less likely to have DTC compared to old age (≥70 years) which was not statistically significant (AOR-0.96, 95% CI 0.16-5.64, P=0.968).In this present study it was observed that out of 159 patients were BTN among them 6 were diagnosed as carcinoma and 153 were diagnosed as benign thyroid nodule detected by FNAC. Sixty-nine patients were DTC among them 9 were diagnosed as benign and 60 were diagnosed as carcinoma thyroid nodule detected by FNAC. Out of 69 patients were DTC among them 42 were predicted as DTC and 27 were predicted as benign thyroid nodule detected by serum TSH. Out of 159 patients were BTN among them 127 were predicted as BTN, whereas 32 were predicted as DTC detected by serum TSH.In this series, acceptable sensitivity, specificity, PPV, and NPV had been achieved (sensitivity 86.96%, specificity 96.2%, PPV 90.90% and NPV 94.44%) diagnosed by FNAC.Diagnostic FNAC results are obtained in approximately 80% of the cases and repeat aspiration can augment the accuracy of the procedure.[28,29]In this study it was observed that sensitivity of TSH was 60.87%, specificity was 79.87%, PPV was 56.76% and NPV

was 82.47%. Almost similarly observation conducted by Dorangeet al.[30]where they reported that sensitivity of TSH was 55.0%, specificity 77.0%, PPV 70% and NPV 63.0%.

V. Conclusion

The risk of differentiated thyroid carcinoma in thyroid nodules increased with increased serum TSH concentration even within the normal range. Serum TSH could serve as an adjunct to other well defined clinical parameters and FNAC in predicting the risk of differentiated thyroid carcinoma in patients presenting with thyroid nodule(s). This may be important because of the simplicity and availability of the measurement of serum TSH.

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