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Thyrotropin Hormone Level as Predictor for Papillary Thyroid Carcinoma in Patients with Thyroid Nodule

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Objective: To assess thyrotropin hormone level as predictor of papillary thyroid carcinoma.

Design: A Retrospective Study.

Setting: Salmaniya Medical Complex, Bahrain.

Method: Biochemical results of thyroid function, FNAB and histological reports of 319 patients (277 females and 42 males) were retrospectively evaluated.

Result: Thirty-seven (11.6%) patients had papillary thyroid carcinoma (PTC) and 282 (88.4%) patients had benign multinodular goiter (BMNG). Twenty-eight (10.1%) had PTC in females on final histopathology diagnosis and 9 (21.4%) in males, both genders had thyroid nodule, (P<0.05). The mean TSH level was 5.85 mIU/L (±20.6). The mean TSH level was significantly higher in patient with PTC than those having benign thyroid disease (BTD) (P<0.0001). Subgroups analysis revealed no statistically significant difference among patients harboring PTC and those diagnosed as BTD.

Conclusion: High incidence of PTC is associated with TSH above the clinical reference range. It is recommended that patients with TSH in the upper reference range should be subjected to FNAB for possible carcinoma.

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Thyroid cancer is common endocrinological malignancy, accounting for approximately 1% of all new malignancies and its incidence is increasing[1,2]. Recognized risk factors for thyroid malignancy include young above 20 years or more than 70 years, male gender and history of irradiation exposure[3,4]. Predictors of malignancy in thyroid nodules include the hard and fixed lesions on clinical examination, rapidly growing nodules, associated hoarseness, dysphagia or lymphadenopathy; however, most of these symptoms and signs are relatively uncommon at diagnosis[5,6]. Moreover, thyroid gland harboring malignancy is clinically indistinguishable from those that do not. The most challenging issue to clinicians is to identify those minorities who have malignancy and who would require early surgical intervention[7].

Fine needle aspiration biopsy (FNAB) is the gold standard and the most cost-effective method of determining the nature of a thyroid nodule[8]. Its diagnostic sensitivity and specificity ranges between 65%-100%, false-positive or false-negative results reported in about 5%[9,10]. Its results are non-diagnostic or indeterminate in only 20%-25% of the cases. To increase its diagnostic efficacy, it could be combined with other investigations such as ultrasonography or other laboratory investigations.

Recently, controversial studies claimed that Thyrotropin (TSH) has a predictive value in papillary thyroid carcinoma (PTC) due to its central role in the regulation of thyroid function and gland growth; however, the issue still remains to be settled**.**

The aim of this study is to evaluate TSH level as a predictor of PTC among Bahraini patients harboring thyroid nodules.

METHOD

Three hundred nineteen patients who presented with thyroid nodules and attended the FNAC clinic or had surgical resection of thyroid nodule were included in the study from January 2009 to December 2013. Laboratory FNAB cytology, histopathology reports, biochemistry results and personal characteristics were documented.

Cases of medullary thyroid carcinoma, lymphoma, and anaplastic carcinoma were excluded because they are not TSH dependent; Hashimoto's thyroiditis and Hurtle cell change were considered as benign thyroid disease (BTD). Reports of malignant cells seen on cytology were labelled positive PTC and were confirmed histologically. False-negative cytology results were defined as one or more diagnostic aspirates without suspicious or malignant features, but histopathology revealed malignancy. Cases were considered to be true-negative if both cytological and histopathology diagnostic results confirm BTD.

Thyrotropin hormone (TSH) was measured using electrochemiluminescence immunoassay "ECLIA" (Roche Elyces analyzer, with a sensitivity of 0.005uIU/L). The reference range for TSH was 0.25-5uIU/L. Patients were divided into four groups according to their TSH levels.

Group 1 included patients with TSH level <0.25uIU/L, group 2 included patients with 0.26-2.2mIU/L, group 3 included patients with TSH levels between 2.3-5mIU/L, and group 4 included those with TSH level >5uIU/L.

Sensitivity, specificity, and positive and negative predictive values of FNAB were calculated according to the final diagnostic outcome which was defined as the presence or absence of PTC. Other statistical analyses were performed using SPSS version 20. Serum TSH and age were considered as continuous variables.

RESULT

Three hundred nineteen patients with thyroid nodule were reviewed. Two hundred seventy-seven (86.8%) patients were females, 42 (13.2%) were males. The minimum age was 16 years and the

maximum was 85 years. The mean age was 45.7 years (±13.3); the mean age of females was 45.1 (±12.8) compared to males 50.1 (±15.8) years.

Thirty-seven (11.6%) patients had PTC and 282 (88.4%) patients had benign multinodular goiter (BMNG). Twenty-eight (10.1%) female patients and 9 (21.4%) male patients had PTC, (P<0.05). The mean TSH for all patients was 5.85 mIU/L±20.6 meaning, the lowest value was 0.0 mIU/L and the highest value was 193 mIU/L. The mean TSH level was 5.8±20.6mIU/L for all patients. TSH mean level was 2.7 (±0.8) mIU/L for patients with BTD whereas it was 29.2 (±53.8) mIU/L in PTC patients. Mean TSH in the female group was 5.8 (±9.4) mIU/L versus 5.6 (±21.8) mIU/L in the male group, see table 1.

Table 1: Gender, Age, TSH and Final Histopathology Diagnosis

			P -value
Gender	Female	277 (86.8%)	$<0.05^{*,a}$
	Male	42 (13.2%)	
Mean age Y (±SD)	All	45.7 (±13.3)	$<0.5^{*,b}$
	Female	45.1(±12.8)	
	Male	50.1(±15.8)	
Histopathology diagnosis (N = 319)	BTD	282 (88.4%)	$< 0.05^{*,a}$
	PTC	37 (11.6%)	
Mean TSH (mIU/L) (±SE)	All	5.85 (±20.6)	$<0.5^{*,b}$
	BTD	2.7 (±0.8)	
	PTC	29.2 (±53.8)	
Mean TSH (mIU/L) (±SD)	All	5.85 (±20.6)	$>0.5^{b}$
	Female	5.8 (±9.4)	
	Male	5.6 (±21.8)	

[(a)] = Chi-Square test, [(b)] unpaired t student test, * = p value < 0.05

The incidence of PTC in females is 2.4 times compared to males (P<0.05), see table 2. Further classification of patients into groups, showed no statistical significance between both genders except at the higher sector of the clinical reference range.

Table 2: BTD and PTC in Different Groups According to Gender

Groups		**Male**	**Female**	**Total**	**F/M Risk**	**P value[(a)]**
<0.25	**BTD**	**6** (100%)	**35** (94.6%)	43 (100.0%)	∞	>0.05
	PTC	**0** (0.0%)	**2** (5.4%)			
	Total	**6** (100%)	**37** (100%)			
0.26-2.2	**BTD**	18 (94.8%)	129 (95.6%)	154 (100.0%)	1.1	>0.05
	PTC	1 (5.2%)	6 (4.4%)			
	Total	**19**	**135**			
2.3 - 5.0	**BTD**	3 (60%)	52 (89.7%)	63 (100.0%)	5.7	$<0.05^{*}$
	PTC	2 (40%)	6 (10.3%)			
	Total	**5**	**58**			
>5.0	**BTD**	6 (50%)	33 (70.3%)	59 (100.0%)	2.3	>0.05
	PTC	6 (50%)	14 (29.7%)			
	Total	**12**	**47**			
Total	**BTD**	33 (78.6%)	249 (89.9%)	319 (100.0%)	2.4	$<0.05^{*}$
	PTC	9 (21.4%)	28 (10.1%)			

Total	**42**	**277**	

[(a)]=Chi-Square test, *=p value < 0.05

The prevalence of PTC was 37 (11.6%). Classifying patients into subgroups according to their TSH level, showed an increase in the prevalence of PTC in parallel with increased TSH level, see table 3. The prevalence in lower TSH level was 4.7% and 4.5% for patients with TSH level in subnormal and lower sector of clinical reference range respectively. This ratio is increased to 12.7% versus 33.9% in the higher sector of clinical reference range and higher TSH level respectively.

Table 3: Distribution of BTD & PTC according to TSH

	Histologic Diagnosis			
TSH level	**BTD**	**PTC**	**Total**	**P value[(a)]**
All	282 (88.4%)	37 (11.6%)	319	<0.05*
<0.25	41 (95.35%)	2 (4.7%)	43	>0.05
0.26-2.2	147 (95.5%)	7 (4.5%)	154	>0.05
2.3-5.0	55 (87.3%)	8 (12.7%)	63	<0.05*
>5.0	39 (66.1%)	20 (33.9%)	59	<0.05*

(a)=Mann-Witney test, *=p value < 0.05,

The mean TSH level was significantly higher in patients with malignancy compared with those having benign thyroid pathology (P<0.05). There was no statistically significant difference in patients with PTC and those diagnosed as BTD in subnormal TSH level, (<0.25mIU/L), as well as those in the lower clinical reference range sector (0.26-2.2mIU/L, P>0.05). There was a statistically significant difference in TSH level among patients having PTC and benign thyroid nodule in the higher sector of the clinical reference range (2.3-5mIU/L, P<0.02) or higher TSH levels (>5.0mIU/L, P<.0001), see table 3.

Binary and stepwise logistic regression analysis revealed that TSH level is predictor of PTC even in association with age and gender, see table 3. However, binary logistic regression revealed that gender rather than age was predictor of PTC. In different patients' subgroups, the same finding is predicted in the high sector of the clinical reference range. Above the clinical reference range, TSH was predictor of PTC either alone or in association with gender. However, gender and age separately were not predictors of PTC, see table 4.

Table 4: Binary Regression and Stepwise Regression: Patients Classified According TSH Level, Gender and Age

TSH (mIU/L)		**OR**	**95% CI**	***P*-value[(d,c)]**
All	TSH	1.1	1.05-1.1	< 0.05[(d)*]
	TSH, gender	1.1	1.04-1.1	> 0.05[(c) *]
	TSH, gender, age	1.1	1.04-1.1	> 0.05[(c) *]
	Gender (F)	0.4	0.17-0.9	> 0.05[(d) *]
	Age	0.9	0.9-1.0	> 0.05[(d)]
<0.25	TSH	3.8	0.0-52209048 (0.0)	> 0.05[(d)]
	TSH, gender	4.1	0.0-544050617 (0.0)	> 0.05[(c)]
	TSH, gender, age	5.9	0.0-155612742 (0.0)	> 0.05[(c)]

	Gender (F)	0.2	0.0	> 0.05[(d)]
	Age	1.0	0.9-1.1	> 0.05[(d)]
0.26 - 2.2	TSH	1.9	0.5 – 7.3	> 0.05[(d)]
	TSH, gender	0.7	0.08-7.0	> 0.05[(c)]
	TSH, gender, age	0.9	0.9-1.0	> 0.05[(c)]
	Gender (F)	0.8	0.09-7.0	> 0.05[(d)]
	Age	0.9	0.9-1.0	> 0.05[(d)]
2.3 - 5.0	TSH	2.8	1.0-7.8	< 0.05[(d)] *
	TSH, gender	2.8	0.02-1.59	< 0.05[(c)] *
	TSH, gender, age	2.8	1.0-8.08	< 0.05[(c)] *
	Gender (F)	0.16	0.02-1.2	> 0.05[(d)]
	Age	0.9	0.9-1.0	> 0.05[(d)]
> 5.0	TSH	1.06	1.0-1.1	< 0.05[(d)] *
	TSH, gender	1.05	1.0-1.1	< 0.05[(c)] *
	TSH, gender, age	1.05	0.99-1.1	> 0.05[(c)]
	Gender (F)	0.4	0.11-1.5	> 0.05[(d)]
	Age	0.9	0.9-1.0	> 0.05[(d)]

(d) = Binary logistic regression analysis

(c) = stepwise logistic regression

* = p value < 0.05, OR = odd ratio, CI = confidence interval

DISCUSSION

Comparison between cytopathology and final histopathology diagnosis revealed true-negative cytological diagnosis of PTC in 283 (88.7%) patients; 27 (8.4%) patients were diagnosed as true positive cytological category. Only 2 (0.6%) of patients who had false-positive result were cytologically diagnosed as malignant. Seven (2.1%) false-negative cytological diagnoses were made. Our FNAB result revealed sensitivity of 79.4%, specificity of 99.3%, positive predictive value of 93.1% and negative predictive value of 97.59%, which were comparable with other studies[9].

TSH in thyroid malignancy is still a matter of controversy. Some studies disagree with its role in initiating and/or promoting the growth of preexisting thyroid cancers. Other studies emphasized the role of other growth factors such as insulin like growth factor-I (IGF-I) as a more potent stimulator of thyroid cancer growth[11,12]. Other studies stated that TSH requires cooperation with insulin/IGF-1 to exert its proliferative effects[13]. In addition, other studies concluded that thyroid cancer is known to occur in thyroid nodule in a thyroid lobe in which activity is suppressed by the hyper-functioning nodules in the other lobe[14]. Other researchers studied TSH receptors signal transduction and found that TSH receptor mutations in regions functionally associated with increased signal transduction do not commonly occur in thyroid carcinomas[15].

In our study, TSH >5.0 mIU/L, remained as an independent predictor either on its own or in association with gender but not with age, which is similar to other studies[16]. Statistical analysis revealed that female gender was at a higher risk of possessing PTC in the overall patient's groups or in subgroups. The highest estimated risk of PTC was at TSH level between 2.3-5 mIU/L, where females had an estimated risk 5 times more than males. Other studies have reported similar findings[17-20].

Boelaert et al found serum TSH concentration as an independent predictor of the presence of thyroid malignancy in addition to patients' age and gender[18]. They confirmed that the lowest risk of malignancy was in patients with subclinical hyperthyroidism (TSH<0.4 mIU/l), and the prevalence of thyroid cancer was high in those with subclinical hypothyroidism (TSH>5.5 mIU/l).

Haymart et al found that the likelihood of malignancy was 16% if TSH was <0.06 mIU/L, 25% if TSH 0.40-1.39 mIU/L, 35% if TSH 1.40-4.99 mIU/L and 52% if TSH 5.0 mIU/l or greater[21]. A study of 50 patients undergoing thyroidectomy has confirmed increased risk of cancer diagnosis in subjects with serum TSH concentrations in the upper three quartiles of TSH values compared with patients whose serum TSH was in the lower quartile[22].

TSH as a predictor of PTC could have several clinical implications. Serum TSH in patients with thyroid nodules may help in diagnosis combined with clinical, radiological, and cytological criteria. Clinicians would be more inclined to perform fine-needle aspiration of nodules in patients with higher serum TSH. Furthermore, thyroid cancer screening could be considered in patients with TSH elevations. Finally, if serum TSH plays a significant role as a causative factor for thyroid cancer, a potentially great benefit would be gained from TSH suppression therapy[22]. It is important to recognize that a suppressed TSH does not rule out a diagnosis of thyroid cancer. In this group, the recent genome-wide association study has indicated that serum TSH concentrations are lower in patients carrying one of two alleles who are at increased risk of PTC[23]. It is prudent to realize that serum TSH alone must not be used for diagnostic decision.

CONCLUSION

High incidence of PTC is associated with TSH above the clinical reference range. It is recommended that patients with TSH in the upper reference range should be subjected to FNAB for possible carcinoma.

The finding of the present study revealed high prevalence of PTC in patients harboring thyroid nodule when their TSH level is above the clinical reference range. Physicians are advised to perform FNAC for those patients with TSH level in the higher sector of clinical reference range as those patients are at high risk for PTC.

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