Pre-operative serum TSH level estimation for predicting malignant nodular thyroid disease

Kotaiba Kh. Hamdi* **FIBMS**
Basim R. Ghadhban** **FJBMS**
Hussein Ali Turkey*** **CABS**
Tharwat I.Sulaiman** **CABS, FRCS, FACS**

Abstract:

Background: the aim of this study was to assess the value of serum thyroid–stimulating hormone (TSH) levels in predicting malignancy in patients with nodular thyroid disease (NTD).

Objective: The aim was to examine the relationship between preoperative TSH and differentiated thyroid cancer (DTC).

Patients and Method: all patients with NTD who were admitted in the first surgical unit of Baghdad teaching hospital and assessed for preoperative TSH level before subjecting them for thyroidectomy from first of April 2014 to 31 of January 2016, were included in the study. A preoperative database sheets including Age, gender, nodule size, and pathology were evaluated. Logistic regression analysis was used to determine which factors were predictive of malignancy.

Results: 291 patients were included in our study after exclusion of 20 patients,
Four patients with histopathological results other than differentiated thyroid cancer (anaplastic, medullary carcinoma) and sixteen patients were on thyroxine therapy.
The overall rate of malignancy was 11%.The rate was slightly higher at extremes of age .the mean TSH was higher in the malignant group (2.07 vs 1.07, p=0.02). The rate of malignancy was 40% in patients with TSH level > 5.5 µIU/mL. Logistic regression analysis revealed that TSH level was the only significant risk factor for malignancy.

Conclusion: the serum TSH level may be useful in predicting the probability of cancer and optimizing the extent of thyroidectomy in patients with NTD.

Keywords: Thyroid stimulating hormone; Thyroid malignancy; Nodular thyroid disease.

Fac Med Baghdad 2017; Vol.59, No.3
Received: May 2017
Accepted: Aug. 2017

Introduction:

Thyroid carcinoma, in most cases, presents clinically as a solitary thyroid nodule or as a dominant nodule within a multinodular thyroid gland. The challenge to clinicians is to identify the minority of thyroid nodules (5-15%) that harbour malignancy. There are a number of well-established predictors of malignancy in thyroid nodules, including the finding of hard and fixed lesions on clinical examination, rapid growth of nodules, associated hoarseness, dysphagia or lymphadenopathy , although all of these symptoms and signs are relatively uncommon at diagnosis1'2 . Several factors including age, sex, nodular size, and a previous history of radiation have been evaluated for their potential in predicting thyroid malignancy. The preoperative serum thyroid-stimulating hormone (TSH) level was evaluated in many studies as an independent predictor of thyroid malignancy in patients with a nodular or diffuse goitre3 and higher serum TSH levels were correlated with a higher incidence of malignancy. It is well known that TSH stimulates thyroid cancer growth, invasion, and angiogenesis so therapy for patients with thyroid cancer includes Supra-physiological doses of thyroid hormones to suppress secretion of TSH from anterior pituitary. Although this has been shown to reduce recurrence and improve survival, whether or not TSH has a role in the development of thyroid cancer is still under study3 . The objective of our study is to evaluate the use of preoperative serum TSH level for predicting thyroid malignancy in patients with nodular thyroid disease in whom benign and malignant disease was confirmed histologically.

* *Alkarkh general hospital kotaibakhalid1981@gmail.com*
***Dept. of surgery, Baghdad University College of medicine*
**** Baghdad teaching hospital*

Patients and Methods:

From the first of April 2014 to 31of January 2016, 311 patients with NTD were subjected to thyroidectomy by a team of a surgeon and his trainees in the first surgical unit of Baghdad teaching hospital. Exclusion criteria were :(1) patients with a final histopathological diagnosis other than differentiated thyroid cancer (e.g., medullary thyroid cancer, anaplastic thyroid cancer, lymphoma of thyroid), (2) hyperthyroidism (3) patients on thyroxine therapy or antithyroid drugs at presentation. Two hundred ninety one patients were eligible for our study. All patients had a nodular goiter either as solitary thyroid nodule or multinodular goiter detected by clinical examination, ultrasound scan (US), or both. Preoperatively, thyroid US confirmed NTD in all cases. Fine needle aspiration (FNA) cytology was performed for

clinically detectable thyroid nodules. FNAC performed for small nodules under US guidance. Cytological results were classified into the following categories: benign, malignant, and indeterminate (follicular neoplasm, hurthle cell neoplasm and suspicious for papillary cancer) and non-diagnostic (insufficient cells for diagnosis).

Demographic data obtained included patient age and gender, nodule size, and final postoperative histopathology. All patients had a serum TSH level measured by a sensitive serum TSH assay. Measurement of TSH concentration was performed by automated immunochemiluminescent assay. The normal range for Serum TSH was between 0.34μIU/mL and 5.5μIU/mL. The level were stratified into 4 groups for comparison based on results of prior studies: (1)<0.9μ IU/mL, (2) 0.9 μIU/mL to 1.7 μIU/mL, (3) 1.8 μIU/mL to 5.5 μIU/mL, (4) >5.5 μIU/mL. Age was evaluated as a categorical variable in 1 of 4 age groups (< 30 years old, 30-49years old, 50-70 years old, and >70 years old) for the purpose of statistical analysis. This analysis is performed to determine whether or not there are differences in age, sex, nodular size, and TSH level between patients diagnosed with benign lesions, compared with those diagnosed with thyroid cancer. SPSS version-20 for windows was used for data entry and analyses, data were presented as mean± SD or percentages and appropriate tests were used [(chi-square (fisher's exact test when it is un-applicable)], independently sample T test and binary logistic regression to analyses the data.

Results:

There were 291 patients who met the inclusion criteria. Two hundred fifty nine patients (89%) proved to have benign nodules and other 32(11%) patients had malignant disease. The results of fine needle aspiration were benign in 78.5%, malignant in 1%, indeterminate in 7.5%, and 13% with non-diagnostic results. As regards to TSH level, the results showed that 36.1% of patients had TSH level of <0.9, 32.6% of patients with level of 0.9-1.7, 29.6% with level of 1.8-5.5, and 1.7% with level of >5.5. Total thyroidectomy was done in 208 (71.5%) of patients, 55 patients (18.9%) had near total, 16 patients (5.5%) lobectomy and 12 patients (4.1%) subtotal thyroidectomy. The histopathological finding revealed that 89.0% of the patients were benign, 6.9% had papillary carcinoma, 1.7% micro-papillary carcinoma and 2.4% follicular carcinoma (table.1). The mean nodule size in the benign group was slightly larger than malignant group (27.93 mm vs 27.06 mm, P=0.7). The rate of malignancy was further analyzed based on patient gender, age, and preoperative serum TSH level. The rate of malignancy in males (14.8%) was higher than in females (10.1%); however the difference was not significant (p= 0.3).The mean age for patients with malignant versus benign pathology was not significantly different (39.2 years vs 40.8 years, p=0.5).

Table.1 Sociodemographic Characteristic, laboratory finding and surgery Type of studied group.

		Count	Column N %
Age category	<30	69	23.7%
	30-49	168	57.7%
	50-70	49	16.8%
	>70	5	1.8%
Gender	Male	54	18.6%
	Female	237	81.4%
FNAC	Benign	228	78.5%
	Malignant	3	1%
	Indeterminate	22	7.5%
	Non diagnostic	38	13%
TSH level	<0.9	105	36.1%
	0.9-1.7	95	32.6%
	1.8-5.5	86	29.6%
	>5.5	5	1.7%
Surgery type	Total thyroidectomy	208	71.5%
	Near total	55	18.9%
	Lobectomy	16	5.5%
	Subtotal thyroidectomy	12	4.1%
Histopathology	Benign	259	89.%
	papillary carcinoma	20	6.9%
	Micropapilary carcinoma	5	1.7%
	Follicular	7	2.4%

When patients were stratified into 1 of 4 age quartiles, there were 69 patients< 30 years of age 10 of them malignant (14.5%), 168 patients between 30 and 49 years 15 of them malignant (8.9%), 49 patients between 50 and 70 years 6 of them malignant (12.2%), and 5 patients >70 years of age 1 patient with DTC (20 %); although there was a tendency towards higher rate of malignancy in patients who were younger than 30 years or older o than 70 years at presentation, the difference was not statistically significant. Most of patients had a serum TSH level within the normal range. The serum TSH levels for study were < 0.9μIU/mL in 105 patients, between 0.9μIU/ml And 1.7 μIU/mL in 95 patients, between 1.8 μIU/mL and 5.5 μIU/m in 86 patients, and > 5.5 μIU/mL in 5 patients. The mean serum TSH level was significantly higher in patients with malignant pathology than in patients with benign pathology (2.07 vs 1.07, P=0.02). The change in the prevalence of DTC with serum TSH concentration was linear. Patients with TSH levels between 1.8μIU/mL - 5.5μIU/mL, and > 5.5μIU/mL had higher rate of malignancy when compared to other categories. (Table 2)

Table 2- TSH level and the incidence of benign and malignant nodular thyroid disease.

TSH level	BENIGN			MALIGNANT			P VALUE
	Count	Column n %	Row n %	Count	Column n %	Row n %	
<0.9	96	91.4%	37%	9	8.6%	28.2%	0.1
0.9-1.7	85	89.5%	32.8%	10	10.5%	31.2%	
1.8-5.5	75	87.2%	29.0%	11	12.8%	34.4%	
>5.5	3	60.0%	1.2%	2	40.0%	6.2%	

Further analysis was constructed to estimate the probability of malignant versus benign disease using serum TSH level and age. Patients with a serum TSH level < 0.9 µIU/mL are the least likely to have malignant tumors (8.6%). Patients with TSH level > 5.5 µIU/mL have a higher likelihood of malignancy (40%). For patients with TSH level between 0.9 - 5.5, we can correlate between TSH level and patient age to predict the risk of malignancy. In Patients with DTC who were < 30 years old, one patient had TSH level < 0.9, 4 patients had TSH level 0.9-1.7, and 5 patients had TSH level 1.8-5.5. So difference is significant between TSH level categories for patients less than 30 years.

Table 3- relationship of age category and TSH level of patients with malignant tumor

		Malignancy		TSH level				P- Value
				<0.9	0.9-1.7	1.8-5.5	>5.5	
Age Category/ Years	<30	malignant	Count	1	4	5	0	0.2
			%within Age category	10.0%	40.0%	50.0%	0.0%	
	30-49	malignant	Count	4	5	4	2	
			%within Age category	26.7%	33.3%	26.7%	13.3%	
	50-70	malignant	Count	4	0	2	0	
			%within Age category	66.7%		33.3%		
	>70	Malignant	Count	0	1	0	0	
			%within Age category	0.0%	100.0%	0.0%	0.0%	

Binary logistic regression analysis including gender, age, and TSH level was performed to determine which factors are independent risk predictors for thyroid malignancy. Significantly increased odds ratio for TSH level between 1.8 and 5.5 was found, whereas age and gender were not found to independently predict the presence of thyroid malignancy.

Discussion:

Serum TSH is a well-established growth factor for thyroid nodules, and suppression of TSH by administering exogenous thyroxine may interfere with the growth of established nodules as well as formation of new thyroid nodules. Thyroxine therapy for TSH suppression after thyroidectomy for DTC is independently associated with reduced recurrence and mortality4. This trophic effect of TSH on thyroid tissue that promotes neoplasia could be a possible explanation for the increased risk associated with higher serum TSH concentration even within normal range. By contrast patients with autonomous hyper functioning thyroid nodules, which are rarely malignant, have low serum TSH levels5. This study supports that serum TSH concentration at presentation is an independent predictor of thyroid malignancy in patients with nodular goitre. We demonstrated that the risk of malignancy increased in parallel with serum TSH concentration at presentation which is in agreement with previously published data by Boelaert et al. Although our study included fewer patients when compared with Boelaert et al (1500 patients). The overall rate of malignancy was 11%, a little higher than Boelaert et al. study of (8.0%). Patients with serum TSH levels < 0.9 in our study had the lowest risk of malignancy. While in patients with higher serum TSH levels, the risk of malignancy increased in a near linear fashion. This pattern was true even for serum TSH increases that occurred within normal range. For patients with TSH level > 5.5, the rate of malignancy was 40 %. This raises the possibility that serum TSH may play a role in the development of malignancy. Although male patients have been shown to have a higher rate of malignancy in prior studies, gender did not significantly affect the rate of malignancy in our study1,2 . Even though the rate of malignancy was higher in men (14.8%). We could not find a statistically significant relation between nodule size and rate of malignancy. Benign nodules were slightly larger than malignant nodules in our study and also in the series by Haymart et al6. Despite the observation of higher rate of malignancy in ages under 30 and over 70 years, as reported elsewhere 3'6'7, the difference was not significant in our study.

FNAC had very low yield in our study, it detected malignancy only in 3 patients and other 5 patients with indeterminate results were found out of 32 patients with malignant disease, In contrast to what was noticed in other series in which sensitivity reached 90%11. This may be due to performing FNAC without U/S guidance.

Conclusion:

The higher serum TSH concentration level within upper limit of normal range is associated with increase in the risk of differentiated thyroid cancer. Serum TSH could serve as adjunct to other well defined clinical parameters and FNAC in predicting the risk of thyroid malignancy and optimizing the extent of Thyroidectomy in patients presenting with thyroid nodules. This may be important because of

simplicity and availability of the measurement of serum TSH.

Authors' contributions:

Dr. Kotaiba Khalid Hamdi: Data collection, data analysis

Prof. Tharwat I. sulaiman: Operated most of the cases, supervisor, literature reviewer

Prof. Basim Rassam Ghadhban: Operated some of cases, literature reviewer

Dr. hussein Ali Turkey: Operated some of cases, literature reviewer

References:

1. *Hegedus L, Bonnema SJ, Bennedbaek FN. Management of simple Nodular goitre: current status and future perspectives. Endocr Rev2003;24:102–32.*

2. Hegedus L. Clinical practice. The thyroid nodule. N Engl J Med2004; 351:1764 –71.

3. Boelaert K, et al. Serum thyrotropin concentration as a novel predictor of Malignancy in thyroid nodules investigated by fine-needle aspiration. J Clin Endocrinol Metab 2006; 91:4295–

4. Pujol P, et al. Degree of thyrotropin suppression as a prognostic Determinant in differentiated thyroid cancer. J Clin Endocrinol Metab1996; 81:4318 –23.301.

5. Polyzos SA, et al. Serum thyrotropin concentration as a biochemical Predictor of thyroid malignancy in patients presenting with thyroid Nodules. J Cancer Res Clin Oncol 2008; 134:953–60.

6. Haymart MR. Understanding the relationship between age and thyroid Cancer. Oncologist 2009; 14:216 –21.

7. Belfiore A, La Rosa GL, La Porta GA, Giuffrida D, Milazzo G, Lupo L, Regalbuto C & Vigneri R 1992 Cancer risk in patients with cold thyroid Nodules: relevance of iodine intake, sex, age, and multinodularity. American Journal of Medicine 93 363–369.

8. Gharib H, Goellner JR, Zinsmeister AR, Grant CS, Van Heerden JA (1984) Fine-needle aspiration biopsy of the thyroid: the problem of Suspicious cytological Windings. Ann Intern Med 101:25–28.

9. Davies L & Welch HG 2006 increasing incidence of thyroid cancer in The United States, 1973–2002. Journal of the American Medical Association 295 2164–2167.

10. Mann K. Evaluation of risk in autonomously functioning thyroid Nodules. Exp Clin Endocrinol Diabetes 1998; 106(suppl 4):S23– 6.

11. Fiore E, Rago T, Provenzale MA, Scutari M, Ugolini C,Basolo F, Di Coscio G, Berti P, Grasso L, Elisei R,Pinchera A & Vitti P 2009 Lower Levels of TSH are associated to a lower risk of papillary thyroid cancer in

Patients with thyroid nodular disease: thyroid autonomy may play a Protective role. Endocrine-Related Cancer 16 1251–1260.

12. McHenry CR, Huh ES, Machekano RN. Is nodule size an independent Predictor of thyroid malignancy? Surgery 2008; 144:1062– 8.

13. Vander JB, Gaston EA, Dawber TR. The significance of nontoxic Thyroid nodules. Final report of a 15-year study of the incidence of Thyroid malign

14. Eng. C. Familial papillary thyroid cancer—many syndromes, too many Genes? J Clin Endocrinol Metab 2000; 85:1755–7.

15. Ron E, Lubin JH, Shore RE, Mabuchi K, Modan Pottern LM, Schneider AB, Tucker MA & Boice JD Jr1995 Thyroid cancer after exposure to External radiation: a pooled analysis of seven studies. Radiation Research 141 259–277.ancy. Ann Intern Med 1968; 69:537– 40.