e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2022; 14(8); 198-208

Original Research Article

An Observational Study of Association between Serum TSH Levels andThyroid Malignancies

Abraham Joseph[1], Kunhambu V[2], Dinulal P P[3], Nabeel MV[3]

[1]Assistant Professor, Department of General Surgery, KMCT Medical College, Manassery, Kozhikode, Kerala

[2]Professor and HOD, Department of General Surgery, ACME, Pariyaram, Kerala.

[3]Assistant Professor, Department of General Surgery, KMCT Medical College, Manassery, Kozhikode, Kerala

Received: 15-06-2022 / Revised: 20-07-2022 / Accepted: 05-08-2022

Corresponding author: Dr. Nabeel M V

Conflict of interest: Nil

Abstract

Background: The prevalence of malignant thyroid malignancies is 5-6% and treatment strategies are almost entirely based on the FNAC results and ultrasound examination. This study is focused on the levels of preoperative serum TSH levels and its co-relation withthyroid malignancies and their clinical presentation and management.

Aim: To study the association between the serum levels of Thyroid stimulating Hormone (TSH) and thyroid malignancies. To study the clinical profile of thyroid malignancies and laboratory results.

Materials: A cross sectional observational study involved 60 patients who were diagnosed with suspected Thyroid Malignancy at the department of General Surgery in ACME Pariyaram. A descriptive analysis of the clinical presentation was done and correlation of preoperative serum TSH level and final histopathology were done. Inclusion criteria, patients with thyroid swelling, Thyroid profile and serum TSH measured before any medical interventions and al the patients included were euthyroid. Patients who were not euthyroid were excluded. Informed written consent was taken and history was taken. FNAC, surgical management, and histopathology follow up was done. Results were arranged and analyzed statistically.

Results: Among the 60 patients 51 were females (85%) and 09 (15%) were males and the female to male ratio was 5.6:1 (Table 1). The mean age of the patients was 42.70±12.82 and ht means TSH levels was 1.97 ± 1.16mlU/L; range from 0.5 to 5.0 mIU/L range taken as the lab standard. The mean duration of the disease noted was 26.6 ± 20.59 months. 07 patients had malignancies; FNAC was positive for papillary carcinoma in 05 (08.3%), 01 (01.7%) follicular carcinoma, 01 (01.7%) medullary carcinoma.

Conclusions: Thyroid malignancies though have varied clinical presentation, the commonest was MNG. The association of preoperative serum TSH levels with malignancy showed a statistically significant correlation (P=<0.01) between higher TSH levels and malignant swellings.

Keywords: Neoplasm, Thyroid, hormone, Radiation and TSH

Background

Thyroid malignancies account for almost 90% of all the endocrine malignances. The treatment strategy has undergone a tremendous change for these malignancies over the past few decades with advent of multidisciplinary approach for diagnosis and management. There has been increase in incidence of thyroid malignancies over the past three decades, however of all the patients who present with thyroid swelling only 5-6 % are malignant.

Detecting malignancy early in these patients and adequate surgical clearance will drastically improve the survival rates. Clinical examination undoubtedly was the first step in the assessment of a thyroid swelling and its clinical features point out a malignant swelling. Thyroid function tests have to be done for all cases followed by fine needle aspiration cytology (FNAC) which is currently the gold standard and primary tool for the detection of thyroid malignancy [1].

Other tests like CT scan, MRI, USG, thyroid scintigraphy help in confirming the diagnosis. Recent studies have found that serum TSH has a clear association with thyroid malignancy [2-5]. Among all the malignancies of endocrine glands, the thyroid cancer accounts for highest prevalence and also the fastest increased prevalence in both genders [6].

Among the thyroid cancers more than 90% were found to be differentiated thyroid cancer (DTC); papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) included [7]. The common clinical presentation of thyroid malignancies was usually nodular goiter, including multinodular goitres and solitary nodules [8].

Signs of rapid growth, fixity, hoarse voice, difficulty in swallowing and lymphadenopathy in male gender aged below 20 and above 80 years indicate malignancy [9].

Tumour staging by Tumour Node metastases (TNM) by the American Joint Committee on Cancer (AIJCC) is used for DTC management all over the world [10].

But understanding the Thyroid malignancy's risk factors is very difficult [11]. Association between exposure to radiation, familial history of thyroid malignancy and benign thyroid diseases are few of the risk factors studied so far [12,13]. Thyrotropin or Thyroid stimulating Hormone (TSH) is the key bio-stimulator in the production of thyroid hormones [12].

Many studies have concluded that patients with higher levels of TSH had the risk of developing Thyroid cancer [13]. On the contrary there are also studies which reported no such significant relationship between TSH levels and thyroid malignancy [14]. The present study was conducted to study the association between the serum levels of Thyroid stimulating Hormone (TSH) and thyroid malignancies. To study the clinical profile of thyroid malignancies and laboratory results.

Materials

A Cross sectional, Descriptive study on 60 patients was conducted at ACME Pariyaram, Department of General Surgery for a period of 18 months from March 2017 to September 2018. The subjects were those attending outpatient departments in Department of General Surgery with Thyroid swelling. An ethical committee approval was obtained and a consent form was used to include the subjects.

Inclusion criteria

Patients with thyroid swelling were included. Patients with thyroid profile and serum TSH measured before any medical intervention was undertaken were included. Patients with euthyroid status alone were included.

Exclusion criteria

Patients who are not willing for surgery were excluded. Patients who are not euthyroid were not included.

The Sample size was based on the study by A. G. Unnikrishnan, Sanjay Kalra, Manash Baruah, Gopalakrishnan Nair, Vasantha Nair, Ganapathi Bantwal, and Rakesh Kumar Sahay [15] with the thyroid swellings prevalence of 12.2% was assumed. Fixing the level of confidence at 90% and 7% absolute precision, the minimum sample size was calculated as 60.

Sampling method: A Consecutive sampling method was used.

Statistical Analysis

Descriptive statistics like frequency, percentage, mean and standard deviation were used. Inferential statistics like t-test and chi-square test were used. A p value of less than 0.05 was considered significant. All the patients were subjected to a detailed clinical history of the patient, Clinical examination, preoperative investigations such as Hemoglobin, TC, DC, ESR, BT, CT, Blood Urea, Serum creatinine and specific investigations like FNAC,

Thyroid function tests, Preoperative indirect laryngoscope examination of vocal cords. Surgery was performed based on the stage and FNAC report of tumor. Correlation of fine needle aspiration cytology, histopathology and serum TSH values was completed.

Statistical Software

The Statistical software namely SAA 9.2 ,

SPSS 15.0, Stata 10.1, Medcale 9.0.1, Systat 12,0 and R environment ver.2.11.1 were used.

Results

This cross sectional descriptive study included 60 patients admitted and treated in the department of general surgery in ACME, Pariyaram during the period March 2017 to September 2018.

The preoperative TSH levels were analyzed with postoperative HPE report to check for any relationship between the TSH levels and the likelihood of the thyroid nodule being malignant.

At the same time a clinical study of the thyroid malignancies was done. The observed results were subjected to statistical analysis the following observations were made. Among the 60 patients 51 were females (85%) and 09 (15%) were males and the female to male ratio was 5.6:1 (Table 1).

The mean age of the patients was 42.70±12.82 and ht mean TSH levels was 1.97 ± 1.16mlU/L; range from 0.5 to 5.0 mIU/L range taken as the lab standard (Table 1).

The mean duration of the disease noted was 26.6 ± 20.59 months. Among the 60 patients 07 had malignancies, and the commonest malignancy picked up by FNAC was papillary carcinoma in 05 (08.3%), 01 (01.7%) follicular carcinoma, 01 (01.7%) medullary carcinomas were identified (Table 2).

Table 1: Showed the gender distribution in the study (n-60).

Variable	Number	Percentage
Gender		
Male	**09**	**15.0**
Female	51	85.0
Age	42.70±12.82	--
Mean TSH Level	01.97±1.16	--

Pain		
Present	**06**	**10.0**
Absent	54	90.0
Swelling		
Present	**60**	**100**
Absent	0	0
Dyspnoea		
Present	**03**	**5.0**
Absent	57	95.0
Dysphagia		
Present	**01**	**01.7**
Absent	59	98.3
Solitary nodule thyroid		
Left lobe	**06**	**10.0**
Right lobe	**08**	**13.3**
Absent	46	76.7
Multi nodular Goiter		
Present	**44**	**73.3**
Absent	16	26.7
Neck nodes		
Absent	**60**	**100**
Present	0	0
Distant Metastases		
Absent	**60**	**100**
Present	0	0

Table 2: Showed the various reports of FNAC (n-60).

FNAC Reports	Frequency	Percent
Colloid Goiter	13	21.66
HT	01	01.7
Lymphocytic Thyroiditis	06	10.0
Medullary carcinoma	**01**	**01.70**
Multinodular Goiter	33	55.0
Papillary Carcinoma	**05**	**08.3**
Follicular carcinoma	**01**	**01.70**
Non-malignant	53	100.0
Total Malignant	07	11.66
Total	60	100

Among the 60 patients 07 (11.6%) had malignant thyroid lesions which included 05 (08.3%) papillary carcinoma, 01 had (01.7%) follicular carcinoma and 01 (0.1.7%) had medullary carcinoma (Table 3).

Table 3: Showed the Histopathology reports in the study (n-60). (HT: Hyperthyroidism)

HISTOPATHOLOGY	Frequency	Percent
Colloid Goiter	13	21.7
Follicular Carcinoma	**01**	**01.7**
HT	01	01.7
Lymphocytic Thyroiditis	06	10.0
Medullary carcinoma	**01**	**01.7**

Multinodular Goiter	33	55.0
Papillary Carcinoma	**05**	**08.3**
Total	60	100.0

The patients with malignancy had their TSH values showing a significant association with each other (p value was <0.05), (Table 4).

Table 4: Showed the Association between serum TSH levels and Histopathology reports in the study (n-60)

Histopathology	Mean± SD	p value
Colloid Goiter	1.77±1.24	0.710
Follicular Carcinoma	1.70±0.00	
Colloid Goiter	1.77±1.24	0.710
HT	1.24±0.00	
Colloid Goiter	1.77±1.24	0.096
Lymphocytic Thyroiditis	2.83±1.42	
Colloid Goiter	1.77±1.24	0.901
Medullary carcinoma	1.45±0.00	
Colloid Goiter	1.77±1.24	0.735
Multinodular Goiter	1.64±.78	
Colloid Goiter	1.77±1.24	0.016*
Papillary Carcinoma	3.84±1.00	
Follicular Carcinoma	1.70±0.00	0.317
HT	1.24±0.00	
Follicular Carcinoma	1.70±0.00	0.317
Lymphocytic Thyroiditis	2.83±1.42	
Follicular Carcinoma	1.70±0.00	0.317
Medullary carcinoma	1.45±0.00	
Follicular Carcinoma	1.70±0.00	1.000
Multinodular Goitre	1.64±.78	
Follicular Carcinoma	1.70±0.00	0.143
Papillary Carcinoma	3.84±1.00	
HT	1.24±0.00	0.317
Lymphocytic Thyroiditis	2.83±1.42	
HT	1.24±0.00	0.317
Medullary carcinoma	1.45±0.00	
HT	1.24±0.00	0.599
Multinodular Goiter	1.64±.78	
HT	1.24±0.00	0.143
Papillary Carcinoma	3.84±1.00	
Lymphocytic Thyroiditis	2.83±1.42	0.317
Medullary carcinoma	1.45±0.00	
Lymphocytic Thyroiditis	2.83±1.42	0.047*
Multinodular Goiter	1.64±.78	
Lymphocytic Thyroiditis	2.83±1.42	0.201
Papillary Carcinoma	3.84±1.00	
Medullary carcinoma	1.45±0.00	0.834
Multinodular Goiter	1.64±.78	
Medullary carcinoma	1.45±0.00	0.143
Papillary Carcinoma	3.84±1.00	

Multinodular Goiter	1.64±.78	0.001*
Papillary Carcinoma	3.84±1.00	

*Significant at 5% level

Among the 60 patients 36 (60%) showed serum levels of TSH between 1.4 and 4.99 ml U/L, 22 patients (36.66%) had serum levels of TSH between 0.4 and 1.39 ml U/L, 02 patients (03.3%) the serum TSH levels were above 4.99 ml U/L (Table 5).

Table 5: Showed serum TSH levels of the patients studied (n-60).

TSH group	Frequency	Percent
0.4-1.39	22	37.9
1.4-4.99	36	62.1
➢ 4.99	02	03.33
Total	58	100.0

The serum TSH levels in men were ranging from 1.4 to 4.99 ml U/L in 08 (88.88%) and 0.4 to 1.39 ml U/L in 01 (11.11%). Among the 51 females of this study, in 29 (56.86%) the serum TSH values was 1.4 to 4.99 ml U/L and in 22 (43.13%) the values were 0.4 to 1.39 ml U/L (Table 6). Totally 37 patients (61.66%) had serum TSH values between 1.4 to 4.99 ml U/L and in 23 patients the values were 0.4 to 4.39 ml U/L (Table 6).

Table 6: Showed the serum TSH levels range among the study group (n-60).

			TSH group		Total
			0.4-1.39	1.4-4.99	
Sex	Male	Count	01	08	09
		% within Sex	11.11%	88.88%	100.0%
	Female	Count	22	29	51
		% within Sex	43.13%	56.86%	100.0%
Total		Count	23	37	58
		% within Sex	38.33%	61.66%	100.0%

The 07 patients with malignancy showed serum TSH levels between 1.4 and 4.99 in all (100%), (Table 7). Inference- higher TSH values are associated with significantly higher incidence ofmalignancy (Table 7).

Table 7: Showed the Incidence of malignancy according to TSH values our study

TSH values	No. of patients with Malignancy	Percentage
0.40-1.39	0	0
1.40-4.99	7	100
>5.0	0	0

Discussion

Several risk factors as predictors for the development of thyroid malignancy have been identified such as history of previous radiation exposure especially during childhood was known to be found in many cases of thyroid carcinoma. Other environmental risk factors such as excess dietary intake of iodine, vitamin E, and retinol have been shown to have an increased risk of developing thyroid malignancies. Younger age groups (< 20 years) and older groups (> 70 years) are shown to have higher risk of malignancies. Inherited syndromes such as familial

polyposis coli, gardener's syndrome and cowden's syndrome were associated with medullary carcinoma of thyroid. Malignancy should always be suspected in the presence of certain signs and symptoms such as hard and fixed swelling, large swelling (>4cms), presence of neck nodes, rapid increase in the size of the swelling, associated hoarseness of voice, dyspnoea, dysphagia symptoms. Central hyper vascularity, micro-calcifications less than 2mm, irregular borders and invasion into surrounding tissue were the Ultrasound features suspicious of malignancy. Ultrasound scan was more sensitive than clinical examination in the detection of enlarged cervical nodes. Lymph nodes infiltrated by papillary carcinoma may appear as entirely cystic mimicking other cystic swelling of the neck such as branchial cysts. Calcifications may be seen in nodes infiltrated by medullary carcinoma. As TSH was a known thyroid growth factor and well differentiated thyroid cancers express TSH receptors and many studies have shown a definite relationship between preoperative serum TSH levels and malignancy. Furthermore, TSH levels were higher in patients with more aggressive tumours. Although oncogenes and other factors were involved in the pathogenesis of thyroid malignancy, since well differentiated thyroid cancers have TSH receptors, it seems probable that TSH can act as a cancer stimulus. This hypothesis was supported by the improved survival rates seen in patients on levothyroxine suppressive therapy and by cases of tumour growth post T4 withdrawal or recombinant TSH administration. Some studies have shown higher TSH levels associated with advanced stage of thyroid cancer. An increased incidence of thyroid cancer was seen in patients with antibody evidence of Hashimotto's thyroiditis, also supports the role of TSH receptor in the pathogenesis of thyroid malignancies. Previous history of radiation exposure also remained as a risk factor for thyroid malignancies and supported by various authors [16]. The present study: 60 Patients with thyroid swelling suspicious of malignancy were studied. Only euthyroid patients were included. The main objective was study of association between TSH and thyroid malignancy.Of the patients confirmed with malignancy by histopathology a descriptive analysis of the clinical presentation and the management was done. The observations and the results were subjected to statistical analysis and compared with other studies. This study showed out of 09 male patients and 51 female patients out of 60 patients, 07 patients turned out to have malignancy. This distribution was comparable to other studies (Table 8).

Table 8: Comparison of gender distribution of malignant cases with other studies (n-60).

Present study	Jemal *et al* [17]	Dorairajan *et al* [18]	Chennai cancer Institute [19]	P value
3:0	3:1	3.5:1	3.2:1	P<0.001

The mean age at which the malignancy was encountered was compared with other studies and found that the mean age in the present study was 60 years. In a study by Fiore *et al* [21], it was 45 years and in Haymart *et al* [3] it was 46 years (Table 9)

Table 9: Comparison of mean age of malignancy with other studies (n-60)

Present study	Fiore *et al* [20]	Haymart *et al* [3]
60	45	46

In the present study none of the patients had a history of direct exposure to risk factors such as radiation exposure, family history, high iodine diet and goitrogens. Higher incidence of malignancy was seen in the advanced age group; above 65 years. In the present study, most of the patients presented with rapidly growing thyroid swelling of duration of 1 to 2 years.

Some patients had thyroid swelling for more than a decade and presented with a recent change in size or appearance of certain new symptoms. A sudden rapid increase in the size of a thyroid swelling or any compressive symptoms such as dyspnea, dysphagia, dysphonia or Horner's syndrome is suggestive of a malignant change [23].

In the present study the most common presenting symptom was a thyroid swelling; 05 patients presented MNG (multi-nodular Goiter). 01 presented with a dominant nodule in a multi-nodular goiter and 01 with solitary nodule. The next common complaint was pain and discomfort in the neck. Some of the patients had compressive symptoms in the form of dyspnea, dysphonia and dysphagia. In the present study cervical lymphadenopathy was a common presentation with thyroid malignancy Goiters. Approximately 33% to 61% of patients with papillary carcinoma will have involvement of clinically apparent cervical lymph nodes at the time of diagnosis [24]. The incidence of cervical neck nodes in the present study was 0% (Table 10).

Table 10: Showed the comparison of incidence of cervical lymph node involvement with other studies (n-60)

Present study	Mazzaferri *et al* [21]	Dorairajan *et al* [18]	Chennai cancer Institute [19]
0%	33-61%	26-50%	59%

Histopathology

In this study all the malignant tumours of thyroid were well differentiated carcinomas with papillary carcinoma being the commonest followed by follicular carcinoma (Table 10)

Table 11: Comparison of histopathological types of malignancy with other studies

	Papillary ca	Follicular
Present study	71.4%	14.2%
Haymart *et al* [3]	87 %	07%
Bailey & love [1]	60%	20%
Devita *et al* [22]	80-85%	10%
Mazzaferri *et al* [21]	70-80%	10%

In this study the mean preoperative serum TSH value was: 2.39±1.03mU/L. This was comparable to the results of Haymart *et al* [3] Fiore *et al* and joklass *et al*.

Table 12: Comparison of mean TSH value in benign vs malignant disease

	Benign disease	**Malignant disease**	**P value**
Our study	1.80±1.03	3.71±1.22	P<0.001
Haymart *et al* [3]	1.4±0.4	3.7±2.3	P<0.0001
Fiore *et al* [20]	0.70±0.6	1.10±0.6	P<0.0001

On analysis of the preoperative TSH values it was observed that TSH level had a definitive association with malignancy. The following table shows the various studies that have shown a relationship betweenserum TSH concentration and thyroid cancer

Table 13: Summary of studies investigating the relationship between serum TSH level and thyroid cancer

Authors	Journal	No. of patients	Country	Significant findings
Boelaert *et al*. (2006) [2]	Journalof clinical endocrinology and Metabolism	1500	UK	Serum TSH is independent predictor of malignancy in thyroid Nodules. Risk of malignancy rises in parallel with serum TSH within normal range.
Haymart et al.(2008a) [3]	Journal of clinical endocrinology and Metabolism	843	US	Likelihood of thyroid cancer increase with higher TSH Concentration. Higher Serum TSH associated with advanced stage differentiated thyroid cancer
Polyzos et al.(2008) [5]	Journal of cancer Research and Clinical Oncology	565	Greece	Higher rates of thyroid malignancy in patients with TSH in upper percentile of normal range
Haymart *et al*. (2008b) [3]	Clinical endocrinology	1361	US	Thyroid cancer incidence correlates with serum TSH independent of age. Higher TSH is associated with extra-thyroidal extension of disease.
Fiore *et al*. (2009) [20]	Endocrine related cancer	10178	Italy	Higher TSH in patients with T3-T4 disease and inthose with lymph node metastasis

Conclusion:

Thyroid malignancies though have varied clinical presentation, the commonest was MNG. The association of preoperative serum TSH levels with malignancy showed a statistically significant correlation (P=<0.01) between higher TSH levels and malignant swellings. Association of TSH with poorly differentiated carcinoma could not be assessed as all the patients in this series had well differentiated carcinoma. However, as all patients with a thyroid swelling undergo a thyroid function test, it is important to pay special attention to the TSH values. In cases of raised TSH levels in clinically suspected malignant thyroid swelling with a benign FNAC report the FNAC can be relooked to confirm the diagnosis.

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