Original Research Article

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A study of association between serum thyroid stimulating hormone concentration and thyroid cancer and also to assess whether serum thyroid stimulating hormone levels are of value in predicting malignancy in patients with thyroid swelling

Benny Bright*, Joe Mathew, Jacob P. Thomas, Robinson George

Department of Surgery, Pushpagiri Institute of Medical Sciences and Research Centre, Tiruvalla, Kerala, India

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*Correspondence: Dr. Benny Bright,

E-mail: bennybright45@gmail.com

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ABSTRACT

Background: Thyroid neoplasm includes both benign and malignant tumors arising in the thyroid gland. Although thyroid cancer accounts for less than 1% of all cancers, the challenge to clinicians is to identify the minority of thyroid nodules that harbor malignancy. There are a number of well-established predictors of malignancy in thyroid nodules. More recently a few studies have suggested that higher concentration of thyroid stimulating hormone (TSH), even within the normal range are associated with subsequent diagnosis of thyroid cancer in patients with thyroid nodules and even higher serum TSH levels have been found associated with advanced stages of thyroid cancer.

Methods: A prospective study was conducted on 220 cases without overt thyroid dysfunction attending Department of general surgery, Pushpagiri institute of medical science, Thiruvalla.

Results: In our study incidence of malignancy of thyroid carcinoma was highest in patients with serum TSH concentrations, in range of 3.5 mIU/l-5.25 mIU/l, 55 patients out of 220 patients. Individually, incidence of papillary carcinoma (PC) (36/55 patients), follicular carcinoma (FC) (17/55 patients) and Hurthle cell carcinoma (HCC) (2/55 patients) were more in patients with higher TSH. So, from the study it can be clearly state that elevated TSH can be used as an independent predictor of thyroid malignancy. Higher TSH values are associated with papillary thyroid carcinoma.

Conclusions: An elevated TSH can be used as an independent predictor of thyroid malignancy, especially for anticipating a probability of papillary carcinoma of thyroid.

Keywords: TSH, Multinodular goiter, Fine needle aspiration

INTRODUCTION

Thyroid neoplasm includes both benign and malignant tumors arising in the thyroid gland. Although thyroid cancer accounts for less than 1% of all cancers, it is the commonest endocrine tumor. Thyroid cancers are heterogeneous group of tumors with variable rates of growth, biological aggressiveness, histological responses and response to therapy. Thyroid carcinoma in most cases

presents clinically as a solitary nodule or as a dominant nodule within a multinodular thyroid gland.^{3,5} In general population, thyroid nodules are very common with reported prevalence of 4-7% of adults.⁴ The challenge to clinicians is to identify the minority of thyroid nodules that harbor malignancy from the majority which can be managed conservatively. There are a number of well-established of predictors of malignancy in thyroid nodules.⁶ Recently studies have suggested that

higher concentration of TSH, are associated with subsequent diagnosis of thyroid cancer and also with advanced stages of thyroid cancer. Moreover, high TSH levels are seen associated with advanced thyroid malignancy. TSH is an established growth factor for thyroid swellings. Suppression of TSH concentration by exogenous administration inhibit the growth of established nodules and also prevent the formation of new ones. Prospective studies have showed reduction in thyroid cancer related mortality and relapse with aggressive TSH suppressive therapy. Based on these findings it is understood that high rate of cancer with increasing TSH serum levels causes a trophic effect on Thyroid tissue resulting in malignancy. Trophic effect on thyroid gland is mediated by TSH receptors on tumor cells. These findings suggest that TSH play a role in the cause and progression of cancer. Studies shown that high serum TSH concentrations in the upper limit of normal range and in those with abnormally high TSH have increased risk of developing cancer. With the underlying data TSH. May play a crucial role in the development and progression of thyroid carcinoma.

Aim of the study

The aim of the study was to study an association between serum TSH concentration and thyroid malignancy

Objectives

Serum TSH as a predictor of malignancy in patient with thyroid swellings and higher TSH level is associated with an increased risk of papillary carcinoma thyroid

METHODS

This is a prospective and retrospective study on subjects fitted to the inclusion and exclusion criteria.

Study setting

The study was conducted at department of general surgery, Pushpagiri institute of medical science. Thiruvalla.

Study population

All cases of thyroid swellings without overt thyroid dysfunction.

Study period

Study carried out from February 2015 to August 2016.

Inclusion criteria

All cases of thyroid swellings without overt thyroid dysfunction were included in the study.

Exclusion criteria

Patients in whom serum TSH levels were obtained while on thyroid hormone therapy, secondary malignancies in the thyroid (metastasis), thyroid lymphomas, thyroiditis and Grave's disease were excluded from the study.

Methodology used

All patients satisfying the inclusion criteria were included in the study and written informed consent was obtained from all patients included in the study.

Statistical methods

Frequencies: This provides statistics and graphical displays that are useful for describing variables.

Descriptive: This displays univariate summary statistics for several variables in a single table and calculates standardized values.

Chi-square test: Tabulates a variable into categories and computes a chi square statistic. This compares the compared and expected frequencies in each category to test either that all categories contain the same proportion of values/ each category contains a user specified proportion of values.

RESULTS

In our study incidence of malignancy of thyroid carcinoma was highest in patients with serum TSH concentrations, in range of 3.5 mIU/l-5.25 mIU/l, i.e., 55 patients (88.3%) out of 220 patients, correlating higher rates of thyroid malignancy in patients with TSH in upper limit of normal range. Individually, incidence of papillary carcinoma was more in range of serum TSH ranging 4.43 mIU/l-5.25 mIU/l i.e., 36 out of 55 patients, incidence of follicular carcinoma was more in the range of 3.16-4.54 i.e., 17 out of 55 patients and Hurthle cell carcinoma was more in the range of 2.17 mIU/l-3.97 mIU/l i.e., 2 out of 55 respectively. So, from the study it can be clearly state that elevated TSH can be used as an independent predictor of thyroid malignancy. Higher TSH values are associated with papillary thyroid carcinoma

Table 1: Incidence of malignancy.

Histopathology	Frequency	Percentage (%)
Malignancy	55	25.0
Benign	165	75.0
Total	220	100.0

Of the 220 patients, 55 were diagnosed with malignancy (25%)

In our study out of 220 cases of thyroid cancer, incidence of papillary carcinoma-36 (16.4%), follicular carcinoma-17 (7.7%) and Hurthle cell carcinoma-2 (0.9%).

Table 2: Incidence of follicular, papillary and Hurthle cell carcinoma.

Histopathology	Frequency	Percentage (%)
FC	17	7.7
HCC	2	0.9
PC	36	16.4
Benign	165	75.0
Total	220	100.0

Table 3: Mean serum TSH concentrations.

Variables	N	T SH (mIU/l)		T	P	
variables		Mean	SD	value	value	
Malignancy	55	4.30	1.04	6.932	< 0.001	
Benign	165	3.35	0.82	0.932	<0.001	

Maximum number of patients of thyroid carcinoma in our study had serum TSH concentration in upper limit of normal.

Table 4: TSH concentration in various thyroid malignancy.

Variables	N	TSH (mIU/l)		T	P
variables		Mean	SD	value	value
FC	17	3.30	1.14		0.000
HCC	2	3.07	0.90	35,109	
PC	36	4.84	0.41	33.109	
Benign	165	3.35	0.82		
Total	220	3.58	0.97		

Thirty-six patients with papillary carcinoma and 17 patients with follicular carcinoma had serum TSH concentration ranging between 3.30 mIU/l-5.5 mIU/l.

Table 5: Serum TSH and malignancy correlation.

TSH	Histopathology		Total	Consitivity	Cnooificity	PPV	NPV	A garana are
	Malignancy	Benign	Total	Sensitivity	Specificity	EEV	NEV	Accuracy
>3.91	40	42	82	72.7	74.5	48.8	89.1	74.1
>4.05	40	33	73	72.7	80.0	54.8	89.8	78.2
>4.14	39	28	67	70.9	83.0	58.2	89.5	80.0
>4.33	34	14	48	61.8	91.5	70.8	87.8	84.1
>4.56	31	5	36	56.4	97.0	86.1	87.0	86.8

Thirty-one patients out of 55 patients with thyroid carcinoma had serum TSH concentration >4.56 mIU/l. With increasing TSH concentration the incidence of malignancy was found to be increasing. Sensitivity obtained for rising TSH concentration was 56.4, but the specificity was 97 with an accuracy of 86.8.

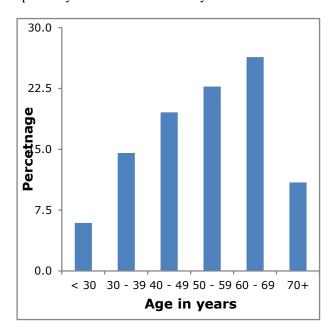


Figure 1: Age distribution.

Maximum number of patients in the study fell into 60-69 years age group (26.4%) and 50-59-year age group (22.7%).

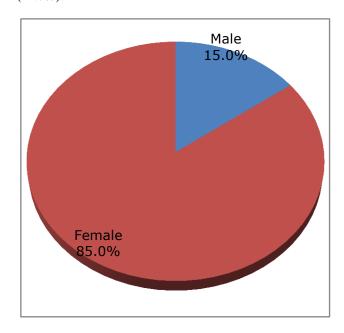


Figure 2: Sex distribution.

In our study maximum incidence of thyroid carcinoma was seen in female patients 187 patients (85%).

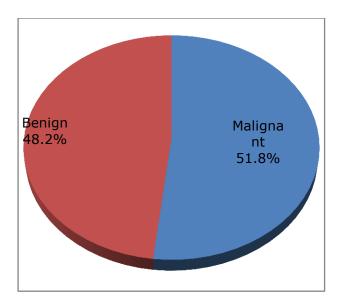


Figure 3: Pre-operative diagnosis.

Of the study group 114 were pre operatively suspected with malignant (51.8%).

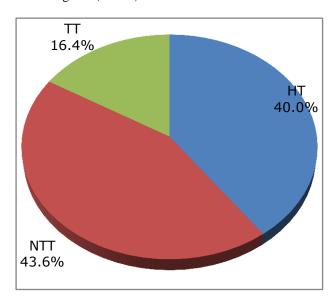


Figure 4: Surgery done.

The 88 patients had solitary nodule and underwent hemithyroidectomy (40%), 96 were having multinodular goiter (MNG) and underwent near total thyroidectomy.

DISCUSSION

Thyroid enlargement is a common clinical problem. Most patients with thyroid enlargement can be managed conservatively after malignancy is ruled out. Thyroid cancer is the most common endocrine malignancy and its incidence continues to rise. ^{1,5} Thyroid carcinoma, in most cases, presents clinically as a solitary nodule or as a dominant nodule within a multi nodular thyroid gland. In the general population, thyroid nodules are very common with reported prevalence of palpable nodules in 4-7% of

adults (0.5% of cancers in men and 1.5% in women).^{2,9} In most cases, thyroid glands harboring malignancy show features of thyroiditis and are clinically indistinguishable from those that do not, and physical examination is therefore deemed largely unhelpful in identifying those patients with thyroid cancer. ¹⁰ 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 suspicion for malignancy include young (<20 years) or old age (>70 years), male gender, large (>4 cm) or rapidly growing nodules (especially during thyroid hormone therapy), and radiation exposure history. It has been widely perceived that rates of malignancy are higher in subjects with solitary nodules than in those with multinodular goiters, although some of the studies have reported similar rates in these two groups. 11 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. 14 Moreover, higher serum TSH levels have been found associated with advanced stages of thyroid cancer. TSH is a wellestablished growth factor for thyroid nodules, and suppression of serum TSH concentrations administering exogenous thyroid hormone may inhibit the growth of established nodules as well as the development of new thyroid nodules. Moreover, therapy with suppressive doses of thyroxine (T4) has long been known to positively affect outcomes in differentiated thyroid cancer and retrospective studies have shown that TSH suppression is an independent predictor of recurrence of differentiated thyroid cancer. Prospective studies have indicated reductions in thyroid carcinomarelated death and relapse with aggressive TSH suppression, especially in high-risk patients. Based on these findings, it is plausible that the higher rates of malignancy with increasing serum TSH concentrations reflect a tropic effect of TSH on thyroid tissue promoting neoplasia and carcinogenesis. These findings suggest that TSH may play a central role in the development and/or progression of thyroid carcinomas. 19 Although oncogenes and other growth factors are involved in thyroid cancer growth and development, it seems probable that TSH can act as a cancer stimulus. This hypothesis is supported by improved survival in thyroid cancer patients treated with suppressive doses of levothyroxine and by cases of tumor growth post-T4 withdrawal or recombinant TSH. 12 It is documented that TSH has a trophic effect on thyroid cancer growth, which is most likely mediated by TSH receptors on tumor cells, and furthermore that TSH suppression is an independent predictor of relapse-free survival from differentiated thyroid cancer¹³. Studies have shown that the risk increases, associated with serum TSH concentrations in the upper half of the normal range, and even more strikingly in those whose TSH measurements were above normal, may at least in part be mediated by this trophic effect of TSH. An alternative explanation is that patients with lower concentrations were developing autonomous function,

which is itself associated with lower rates of malignancy. ²⁰ Considering serum TSH concentration as an independent predictor of thyroid malignancy, studies have predicted probability of diagnosis of thyroid malignancy, increases from less than 10% for serum TSH concentrations at the lower end of the normal range up to 25% if the same patient has a TSH concentration at the upper end of the normal range.

With the underlying hypothesis that TSH, a known thyroid growth factor, may have a fundamental role in thyroid cancer development and progression, we looked at the association between serum TSH concentration and thyroid cancer.

Age

In the study by Jin et al the highest incidence was seen in age group below 30 years. In our study the incidence of malignancy was noted highest in the age group 60-69 year (26.4%).

Cancer type

In the study by Jin et al the final histopathology report was follicular carcinoma-12 (9%), papillary carcinoma-113 (87%), Hurthle cell carcinoma-5 (4%). In our study the incidence of follicular cancer was 17 (7.7%), papillary carcinoma-36 (16.4%) and Hurthle cell carcinoma-2 (0.9%).

Serum TSH concentrations

In study done by Boelaert et al concluded that the risk of diagnosis of malignancy rose in parallel with the serum TSH at presentation, with significant increases evident in patients with serum TSH greater than 0.9 mU/liter, compared with those with lower TSH. Binary logistic regression analysis revealed significantly increased adjusted odds ratios (AORs) for the diagnosis of malignancy in subjects with serum TSH 1.0-1.7 mU/liter, compared with TSH less than 0.4 mU/ liter [AOR 2.72, 95% confidence interval (CI) 1.02-7.27, p=0.046], with further increases evident in those with TSH 1.8-5.5 mU/liter (AOR 3.88, 95% CI 1.48-10.19, p=0.006, compared with TSH<0.4 mU/liter) and greater than 5.5 mU/liter (AOR 11.18, 95% CI 3.23-8.63, p<0.001, compared with TSH<0.4 mU/liter).

In another study done by Polyzos et al higher rates of malignancy were observed in patients with serum TSH concentration in upper limit of normal range, binary logistic regression analysis revealed significantly increased adjusted odds ratio for the diagnosis of malignancy in patients with serum TSH 1.5- 4.0 mIU/l when compared to those with either TSH 0.4-0.8 mIU/L or TSH 0.9-1.4 mIU/l. ¹⁸

The association between serum TSH and risk of thyroid cancer has been proposed by Franklyn and co-workers. In

the first study, a no significant trend toward decreased cancer risk was found in patients with serum TSH below the normal range in a series of 1005 patients submitted to fine needle aspiration (FNA) biopsy of thyroid nodules. In a second study published in 2006 evaluating a series of 1500 patients submitted to FNA, the authors found that the risk of malignancy increases with serum TSH concentrations, i.e., the likelihood of thyroid cancer being higher in patients with higher serum TSH levels, even when TSH values were within normal ranges.

Haymart et al in a series of 843 patients submitted to thyroid surgery, reported a frequency of differentiated thyroid cancer of 16% when TSH was less than 0.06 mIU/liter and 52% when TSH was higher than 5.00 mIU/liter.¹⁷

In another study done by Polyzos et al higher rates of malignancy were observed in patients with serum TSH concentration in upper tertial of normal range, binary logistic regression analysis revealed significantly increased adjusted odds ratio for the diagnosis of malignancy in patients with serum TSH 1.5- 4.0 mIU/l when compared to those with either TSH 0.4-0.8 mIU/L or TSH 0.9-1.4 mIU/l. ¹⁸

CONCLUSION

This was both prospective and retrospective study done to study an association between TSH concentration and Thyroid cancers. Our study also aimed at utilizing serum TSH in predicting the kind of thyroid malignancy.

All patients in our study were clinically assessed with measurement of serum TSH concentration at presentation. These patients underwent HT, near-total thyroidectomy (NTT) and total thyroidectomy (TT) depending upon the clinical evaluation and pre operative investigations. These specimens were sent for histopathological examination.

The final HPR was correlated with the TSH values initially obtained.

In this study we are able to notice that the risk of malignancy rises in parallel with serum TSH within normal range, and even high levels of serum TSH concentrations. Mean TSH level was 4.30 mIU/l in the malignant group compared to a mean TSH of 3.35 mIU/l in the benign group.

In our study maximum number of thyroid cancer patients who had papillary carcinoma had serum TSH concentrations ranging 4.43 mIU/l-5.25 mIU/l i.e., within normal range but towards higher range. Even mean serum TSH concentrations in other carcinomas were in the normal limits but was towards higher range.

With this study and correlating many earlier studies on relationship between thyroid carcinoma and serum TSH

concentration, we are able to conclude that higher rate of thyroid malignancy was observed in patients with higher serum TSH concentration. This is actually caused by the tropic effect of TSH on thyroid tissue that promotes neoplasia and carcinogenesis.

Hence, we conclude that Baseline serum TSH concentration can be used as a biochemical predictor of thyroid cancer in patients with thyroid swelling. And also, we state that high serum TSH concentration in patients with thyroid malignancy can signify an advanced cancer stage at diagnosis

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Institutional Ethics Committee

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