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Original Research Article

Comparative study on association between serum TSH concentration and Thyroid cancer

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ABSTRACT

Background: In India, thyroid cancer accounts for less than 1% of all malignancies (2% of women and 0.5% of men). Thyroid cancer is responsible for 6 deaths per 1 million persons annually. Serum TSH is a well-established growth factor for thyroid nodules, however its role in thyroid malignancy is inconclusive hence this study was conducted with the objective to determine the association between serum Thyroid stimulating hormone (TSH) concentrations with thyroid carcinoma.
Methods: Case control study was conducted in a tertiary care centre. 120 Benign and malignant thyroid subjects respectively were included in the study. Newly diagnosed and record based data collection was done. Measurements of serum TSH concentrations were performed by automated immune chemiluminescent assay. Data was analyzed using SPSS 22 version software, Chi-square test was used as test of significance for qualitative data, p value of <0.05 was considered as statistically significant.
Results: Majority of them were females in the age group 26 to 40 years in both the groups and were diagnosed to have solitary thyroid nodule. In malignant thyroid nodules 51.7% were diagnosed to have follicular carcinoma, 46.7% had papillary carcinoma and 1.7% were diagnosed to have Hurthle cell carcinoma. Significant association was observed between TSH levels and diagnosis of thyroid lesions. TSH was raised (>4mIU/L) in 46.6% of malignant nodules and in 15% of benign nodules. Raised TSH had an odds ratio of 4.958 for Thyroid malignancy compared to benign nodules
Conclusions: Higher TSH levels were associated with Thyroid malignancy and the risk of malignancy rises in parallel with serum TSH within normal range, and high levels of serum TSH concentrations was associated with advanced stage of thyroid cancer.

Keywords: Thyroid malignancy, Thyroid nodule, Thyroid stimulating hormone

INTRODUCTION

Thyroid neoplasm includes both benign and malignant tumours arising in the thyroid gland. In India, thyroid cancer accounts for less than 1% of all malignancies (2% of women and 0.5% of men). Thyroid cancer is responsible for 6 deaths per 1 million persons annually. Although thyroid cancer accounts for less than 1% of all cancers, it is the commonest endocrine tumour that shows a geographic variation in the incidence of tumour type and natural history.[1] Thyroid cancers are heterogeneous group of tumours with variable rates of growth, biological aggressiveness, histological responses and response to therapy.

The incidence of thyroid carcinoma in clinically evident solitary thyroid nodules that are surgically resected varies from 15 to 30% in different series. Women in middle age

are about 5 times more commonly affected than men. These tumours also demonstrate a 3:1 female predominance. There are about 30 to 40 new cases of thyroid cancer /million/year, of which annual mortality from thyroid cancer is about 4 to 5 /million/year. Difference between incidence and mortality reflects the favourable prognosis of most thyroid carcinomas. Though these lesions have the potentiality to aggressiveness and metastasis, 90 to 95% of thyroid cancer cases are categorized as well-differentiated tumours arising from follicular cell, have a favourable prognosis.

In thyroid, nodules become palpable, if they increase beyond 1cm in size. 4% of the general population has detectable enlargement of thyroid. Although nodules are common, clinically detectable thyroid cancer is rare. Serum TSH is a well-established growth factor for thyroid nodules and suppression of TSH concentrations by administering exogenous thyroxine may interfere with growth of established nodules as well as formation of new nodules.[2,3] Objective of the study was to determine the association between serum Thyroid stimulating hormone (TSH) concentration with thyroid carcinoma and its significance in management of Thyroid carcinoma, secondly to predict thyroid malignancy by using Serum TSH concentration in patients with thyroid nodules.

METHODS

Case control study design was on used to collect data from the subjects presenting with thyroid nodules. Patients with secondary malignancies of thyroid, thyroid lymphomas, thyroiditis, Grave's disease and patients in whom TSH levels were obtained while on thyroid hormone therapy were excluded from study.120 benign and 120 malignant thyroid subjects were included into the study. Retrospective data was collected from the medical record section, only those subjects with all the necessary data such as preoperative TSH values, pre-operative diagnosis and histopathological diagnosis were included, simultaneously newly detected cases were included during the study period.

Demographic, pathological data (Preoperative FNAC) and serum TSH concentration levels were recorded from these patients. Cytological results were classified into following categories: malignant, indeterminate, follicular neoplasm, Hurthle cell neoplasm and suspicious for papillary cancer.[4] Thyroidectomy was recommended for patients with malignancy, indeterminate cytology and inpatients with rapid increase in size of nodule. Additional management was based on the final surgical pathology.

Demographic data obtained included patient's age and sex, FNA cytology results, nodule size, thyroid profile, final surgical pathology report and stage. All patients had a serum TSH level measured by a sensitive serum TSH assay. Measurements of serum TSH concentrations were performed by automated immune chemiluminescent assay. The normal range of serum TSH was between 0.34 mIU/L and 5.5 mIU/L. The TSH levels were stratified into 4 groups for comparison based on the results of prior studies: 1) < 0.9mIU/L, 2) 0.9mIU/L to 1.7mIU/L, 3) 1.71mIU to 5.5mIU/L and 4) >5.5mIU/L.

Statistical methods

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of frequencies and proportions. Chi-square test was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation. p value of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

RESULTS

In the study 120 malignant and 120 benign thyroid subjects were included. Majority of them were females in the age group 26 to 40 years in both the groups and were diagnosed to have solitary thyroid nodule. Histopathologically among subjects with malignant thyroid nodules 51.7% were diagnosed to have follicular carcinoma, 46.7% had papillary carcinoma and 1.7% were diagnosed to have Hurthle cell carcinoma (Table 1).

Table 1: Profile of subjects in the study.

		Malignant		Benign	
		Count	**Percentage**	**Count**	**Percentage**
Age in years	< 25	09	7.5%	4	3.3%
	26-40	63	52.5%	68	56.6%
	41-60	48	40.0%	48	40%
Gender	Male	33	27.5%	38	68.3%
	Female	87	72.5%	82	31.7%
Preoperative diagnosis	Solitary thyroid nodule	100	83.3%	116	96.6%
	Multinodular goitre	20	16.7%	4	3.4%%

Table 2: Association between TSH levels and thyroid lesion.

		Malignant nodules	Benign nodules	OR	P value
TSH	Raised (>4mIU/L)	56 (46.6%)	18 (15%)	4.958 (2.678, 9.182)	<0.001*
	Normal	64 (53.4%)	102 (85%)		
TSH cut off levels	0.91-1.70	2 (1.7%)	34 (28.3%)		<0.001*
	1.71-5.5	106 (88.3%)	84 (70%)		
	>5.5	12 (10%)	2 (1.7%)		

In the study majority of subjects with thyroid malignancy i.e. 88.3% had TSH of 1.71 to 5.5 mIU/L, 10% had >5.5 mIU/L, 1.7% had TSH of 0.91 to 1.70 mIU/L (Table 1). Significant association was observed between TSH levels and diagnosis of thyroid lesions. TSH was raised (>4mIU/L) in 46.6% of malignant nodules and in 15% of benign nodules. Raised TSH had an odds ratio of 4.958 for thyroid malignancy compared to benign nodules. Based on the previous studies cutoff values of TSH were used. Subjects were divided in to three groups based on TSH. Majority of malignant and benign nodules had TSH in range of 1.71 to 5.5 mIU/L, however 10% of malignant nodules had >5.5 TSH and only 1.7% of benign nodules had TSH >5.5mIU/L. This difference in TSH was statistically significant (Table 2). In the study, out of 100 subjects with solitary thyroid nodule, majority of them 87% had TSH concentration of 1.71-5.5 mIU/l, 11% had >5.5 mIU/l and 2% had 0.91 to 1.7 mIU/l. Similarly, in multinodular goitre 95% had 1.71-5.5 mIU/l, 5% had >5.5 mIU/l. There was no significant association between TSH concentration and preoperative diagnosis of thyroid lesion (Table 3).

Table3: Association between serum TSH concentration and pre-operative diagnosis of thyroid nodule among malignant cases.

		Pre-operative diagnosis		Total
		Solitary Thyroid Nodule	Multi nodular Goitre	
TSH Concentration	0.91-1.70	2 (2%)	0 (0%)	2 (1.7%)
	1.71-5.5	87 (87%)	19 (95%)	106 (88.3%)
	>5.5	11 (11%)	1 (5%)	12 (10%)
Total		100	20	120

$\chi 2 = 1.121$, df = 2, p = 0.571

In the study on HPE 62 subjects had follicular carcinoma, 56 subjects had papillary carcinoma and 2 subjects had Hurthle cell tumor. Out of 62 subjects with follicular tumor, majority 87.5% had TSH of 1.71 – 5.5 mIU/L, out of 56 subjects with papillary carcinoma, majority 87.5% had TSH of 1.71-5.5 mIU/L and 50% of Hurthle cell tumor had TSH of 1.71-5.5 mIU/L. There was no significant association between TSH levels and HPE diagnosis. Mean serum TSH concentration of Stage 1 and 2 was 4.03 mIU/L, and in Stage 3 and 4 was 5.17mIU/L (Table 4).

Table 4: Association between serum TSH concentrations with histopathological diagnoses (HPE) among malignant cases.

		HPE			Total
		Follicular Carcinoma	Papillary carcinoma	Hurthle cell carcinoma	
TSH Concentration	0.91-1.70	2 (3.2%)	0 (0%)	0	2 (1.7%)
	1.71-5.5	56 (90.3%)	49 (87.5%)	1 (50%)	106 (88.3%)
	>5.5	4 (6.5%)	7 (12.5%)	1 (50%)	12 (10%)
Total		62	56	2	120

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. 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). In most cases, thyroid glands harboring malignancy are clinically indistinguishable from those that do not and physical examination is therefore deemed largely unhelpful in identifying those patients with thyroid cancer. 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 yrs) or old age (>70 yrs), 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 goitres, although some of the studies have reported similar rates in these two groups.[5]

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.

Moreover, higher serum TSH levels have been found associated with advanced stages of thyroid cancer. TSH is a well-established growth factor for thyroid nodules and suppression of serum TSH concentrations by 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.[6-8] Prospective studies have indicated reductions in thyroid carcinoma-related 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. 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 or recombinant TSH.[9]

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 cancer.[10-12] 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 the patients with lower TSH concentrations were developing autonomous function, which is itself associated with lower rates of malignancy.

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.

Jonklaas et al, in their study observed that highest incidence of thyroid cancer was seen in the age group less than 30 years (32%).[13] 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 Boelaert K et al, 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 %,).[14] In the present study majority of subjects with solitary thyroid nodule (n= 100, 83.3%) had malignancy, compared to multinodular goitre (n = 20, 16.7%).

In the study by Jonklaas et al, majority of the subjects had papillary carcinoma - 113 (87%), followed by follicular carcinoma - 12 (9%) and Hurthle carcinoma - 5 (4%). 13 were as in the present study majority of them had follicular carcinoma - 62 (51.7%), followed by papillary carcinoma (46.7%) and Hurthle carcinoma (1.7%). This difference in histopathological diagnosis could be due to regional difference or genetic factors in the study subjects.

In the study done by Boelaert K et al concluded that the risk of diagnosis of malignancy rose in parallel with the serum TSH at presentation.[14] 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

1.8-5.5mU/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 tertile of normal range.[15] 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.

In the present study proportion of malignancy was highest in patients with serum TSH concentrations in range of 1.71 mIU/L-5.5 mIU/L, i.e. 106 patients (88.3%) out of 120 patients, correlating higher rates of thyroid malignancy in patients with TSH in upper tertile of normal range. Proportion of papillary carcinoma and follicular carcinoma was more in range of serum TSH ranging 1.71 mIU/L-5.5 mIU/L i.e. 49 (87.5%) out of 56 patients and 56 (90.3%) out of 62 patients respectively.

In the study by, Haymart MR et al, 204 of 239 patients had Stage 1 and 2 thyroid cancer with mean serum TSH concentrations of 3.1 mIU/L and 35 patients of 239 had Stage 3 and 4 thyroid cancer with mean serum TSH concentration of 4.9 mIU/L.[16] In the present study 88 of 120 patients with stage1 and 2 malignancy had mean serum TSH concentrations of 4.03 mIU/L and 31 patients with stage 3 and 4 malignancy had mean serum TSH concentrations of 5.17 mIU/L. TSH findings was similar to the observation made by Haymart MR et al.

CONCLUSION

This study concludes that higher TSH levels were associated with thyroid malignancy and the risk of malignancy rises in parallel with serum TSH within normal range, and high levels of serum TSH concentrations was associated with advanced stage of thyroid cancer. High serum TSH concentration in patients with thyroid cancer patients can signify more aggressive and advanced cancer stage at diagnosis.

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