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Original Research Article

Observational study on association between serum thyroid stimulating hormone and thyroid malignancy

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ABSTRACT

Background: 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. There are a number of well-established of predictors of malignancy in thyroid nodules. More recently studies have suggested that higher concentration of 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. Objectives were to determine the association between serum thyroid stimulating hormone (TSH) concentration and thyroid cancer and to estimate serum TSH levels in different stages of thyroid malignancy.
Methods: A hospital based observational study was conducted in a tertiary care hospital for a period of 2 year. 120 patients presenting with thyroid nodule without an overt thyroid dysfunction during the study period were included in the study. Chi-square was used as test of significance. Independent t test was the test of significance for quantitative data between two groups.
Results: In the study majority of thyroid cancer patients (106 out of 120) had serum TSH concentrations ranging 1.71mIU/L-5.5mIU/L i.e. within normal range but towards higher range. Mean serum TSH concentrations was significantly high in advanced stages of carcinoma. Mean Serum TSH was high in Stage III and Stage IV (5.17±1.36mIU/l) compared to stage I and II (4.03±1.87mIU/l).
Conclusions: The study concludes that TSH levels were in the Upper reference range in majority of thyroid malignancies and high levels of serum TSH concentrations associated with advanced stage of thyroid cancer.

Keywords: Thyroid malignancy, Thyroid nodule, Thyroid stimulating hormone

INTRODUCTION

Thyroid neoplasm includes both benign and malignant tumour arising in the thyroid gland. In the India, thyroid cancer accounts for less than 1% of all malignancies (2% of women and 0.5% of men). Thyroid cancer is responsible for six 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]

The incidence of thyroid carcinoma in clinically evident solitary thyroid nodules that are surgically resected varies from 15 to 30% in different series. Thyroid carcinoma is rare in children and increases in frequency with increasing age. These tumors 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 a year.[1-3]

In general population 4% of them 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.[4-6]

Although there is limited literature to suggest the role of TSH in predicting thyroid malignancies hence this study was undertaken with the following objectives. To determine the association between serum thyroid stimulating hormone (TSH) concentration and thyroid cancer and to predict the role of serum TSH concentration in diagnosis of thyroid malignancy.

METHODS

A hospital based observational study was conducted in a tertiary care hospital for a period of 2 year. Patients presenting with thyroid nodule without an overt thyroid dysfunction to the centre during this period were included in the study. Subjects on thyroid hormone therapy, secondary malignancies in the thyroid (metastasis), thyroid lymphomas, thyroiditis and Grave's disease were excluded from the study. Sample size of 120 was obtained by using Mean TSH among malignant thyroid lesions as 2.5±0.3mIU/L from the study by Haymart MR et al, 7 at 5% absolute error using the formula $n=Z\alpha^2 SD^2/d^2$. 120 consecutive subjects who were diagnosed as thyroid malignancy by HPE were included in the study 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.

Thyroidectomy was recommended for patients with malignancy, indeterminate cytology and in patients 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 were determined. Patients in whom TSH levels were obtained while on thyroid hormone therapy were excluded from study.

Serum TSH level was measured by a sensitive serum TSH assay by automated immune chemiluminescent assay. The normal range serum TSH was considered as 0.34mIU/L to 5.5mIU/L. The TSH levels was stratified into 4 groups <0.9mIU/L, 0.9mIU/L to 1.7mIU/L, 1.8mIU to 5.5mIU/L, >5.5mIU/L for comparison based on the prior studies.

Statistical methods

Data was entered into data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. Chi-square was used as test of significance. Independent t test was the test of significance for Quantitative data between two groups. P-value<0.05 was considered as statistically significant. Informed consent was obtained from all the subjects and Institutional ethical clearance was obtained prior to the start of the study.

RESULTS

In the study 120 subjects presenting with thyroid nodules and diagnosed as thyroid malignancies were included. Of them majority of them were females (72.5%) in the age group 26 to 40 years (44.2%). 83.3% had as solitary thyroid nodule and 16.7% had multinodular goiter. Majority of the lesions were diagnosed in HPE as follicular carcinoma (51.7%) and papillary carcinoma (46.7%). Majority of them had serum TSH in the range of 1.71-5.5mIU/l (88.3%) (Table 1).

Table 1: Profile of subjects in the study.

		Frequency (n=120)	Percentage
Age	<25 years	09	7.5%
	26-40 years	53	44.2%
	41-60 years	48	40%
	>60	10	8.3%
Sex	Male	33	27.5%
	Female	87	72.5%
Preoperative diagnosis	Solitary thyroid nodule	100	83.3%
	Multinodular goiter	20	16.7%
Type of Thyroid carcinoma	Follicular carcinoma	62	51.7%
	Papillary carcinoma	56	46.7%
	Hurthle carcinoma	2	1.7%
Serum TSH Conc.	0.91-1.70 mIU/l	02	1.7%
	1.71-5.5mIU/l	106	88.3%
	>5.51mIU/l	12	10%

In the study out of 100 subjects with Solitary thyroid nodule majority of them had TSH in the range of 1.71 to 5.5mIU/l (87%) and 11% had TSH>5.5mIU/l.

Similarly among the subjects with Multinodular goiter, majority of them had TSH in the range of 1.71 to

5.5mIU/l (95%) and 5% had TSH >5.5mIU/l. There was no significant association between TSH levels and thyroid nodules. However TSH range among all the subjects in the study were in the upper limit of the normal (Table 2).

Table 2: Association between TSH concentration and type of thyroid nodule.

		Pre diagnosis		χ^2, df, p-value
		Solitary thyroid nodule	Multi nodular goiter	
Serum TSH levels	0.91-1.70 mIU/l	2 (2%)	0	1.121, 2, 0.571
	1.71-5.5 mIU/l	87 (87%)	19 (95%)	
	>5.51 mIU/l	11 (11%)	1 (5%)	
Total		100	20	

In the study out of 62 subjects diagnosed as follicular carcinoma, majority (90.3%) of them had TSH in the range of 1.71 to 5.5mIU/l. Similarly, among the subjects diagnosed as papillary carcinoma goiter, majority of them had TSH in the range of 1.71 to 5.5mIU/l (87.5%) and 12.5% had TSH >5.5mIU/l. There was no significant association between TSH levels and thyroid malignancy. However, TSH range among all the subjects in the study were in the upper limit of the normal among all the malignant lesions (Table 3).

Table 3: Association between TSH Concentration, thyroid nodule and histopathological diagnosis.

		Histopathological Diagnosis			χ^2, df, p-value
		Follicular carcinoma (n=62)	Papillary carcinoma (n=56)	Hurthle carcinoma (n=2)	
Serum TSH levels	0.91-1.70 mIU/l	2 (3.2%)	0	0	6.566, 4, 0.1606
	1.71-5.5 mIU/l	56 (90.3%)	49 (87.5%)	1 (50%)	
	>5.51 mIU/l	4 (6.5%)	7 (12.5%)	1 (50%)	
Thyroid nodule	Solitary thyroid nodule (n=100)	45 (72.6%)	54 (96.4%)	1 (50%)	13.68, 2, 0.001*
	Multi nodular goitre (n=20)	17 (27.4%)	2 (3.6%)	1 (50%)	

Table 4: Comparison of serum TSH levels with stage of tumor.

		Serum TSH	P-value
		Mean±SD	
Stage of Tumor	Stage I and II (n=82)	4.03±1.87	0.001033*
	Stage III and IV (n=38)	5.17±1.36	

In the study, out of 62 subjects diagnosed as Follicular carcinoma, 72.6% were solitary thyroid nodule and 27.4% were Multi nodular goiter. Similarly among 56 subjects with papillary thyroid nodule 96.4% were solitary thyroid nodule and 3.6% were multi nodular goiter, 50% of the lesions were solitary and multi nodular in Hurthle cell carcinoma. This observation was statistically significant (Table 3). Mean serum TSH was high in stage III and stage IV (5.17±1.36mIU/l) compared to stage I and II (4.03±1.87mIU/l). This difference was statistically significant (Table 4).

DISCUSSION

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.[4] In many cases, thyroid glands harbouring 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 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. 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.[6-8]

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.

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. 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 TSH concentrations were developing autonomous function, which is itself associated with lower rates of malignancy.[8-14]

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, association between serum TSH concentration and thyroid nodules diagnosed to be malignant was determined.

In the study proportion of thyroid malignancies was high in age group 26-40 years (44%), of them majority were solitary thyroid nodule (83.3%) and 16.7% multinodular goitre. Majority of the nodules were diagnosed to be Follicular carcinoma by histopathological examination. In the study malignant thyroid lesion were highest in patients with serum TSH concentrations, in range of 1.71mIU/L-5.5mIU/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. Individually, incidence of papillary carcinoma and follicular carcinoma was more in range of serum TSH ranging 1.71mIU/L-5.5mIU/L i.e. 49 (87.5%) out of 56 patients and 56 (90.3%) out of 62 patients respectively. Similarly out of 120 patients 82 had Stage1 and 2 with mean serum TSH concentrations of 4.03mIU/L and 38 of 120 patients had stage 3 and 4 had mean serum TSH concentrations of 5.17mIU/L.

Similar findings were observed in the below mentioned studies, in a study by Jonklaas J et al, the highest incidence of thyroid malignancy were seen in age group less than 30 years (32%).[4] In the study by Boelaert K et al, the highest incidence of thyroid malignancy was seen patients presenting with solitary thyroid nodule presenting with a solitary nodule (n=861, 10.8%), compared with those who presented with a diffuse or nodular goiter (n=639, 4.2%,).[6] In the study by Jonklaas J et al the final histopathology report was follicular carcinoma-12 (9%), papillary carcinoma- 113 (87%) and Hurthle carcinoma- 5 (4%), Boelaert K 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 0.9mIU/liter, compared with those with lower TSH.[4,6] 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.[8] Haymart MR et al, observed that 204 of 239 patients had Stage 1 and 2 thyroid cancer with mean serum TSH concentrations of 3.1mIU/L and 35 patients of 239 had Stage 3 and 4 thyroid cancer with mean serum TSH concentration of 4.9 mIU/L.[7]

CONCLUSION

The study concludes that although there is no significant association between thyroid malignancy and TSH levels, TSH levels were in the upper reference range in majority of thyroid malignancies and high levels of serum TSH concentrations associated with advanced stage of thyroid cancer. From the study it is can be concluded that the higher rate of thyroid malignancy observed in patients with higher serum TSH concentration is caused by tropic effect of TSH on thyroid tissue that promotes neoplasia and carcinogenesis. Baseline serum TSH concentration can be used as a biochemical predictor of thyroid cancer in patients with thyroid nodule. High serum TSH concentration in patients with thyroid cancer patients can signify more aggressive and advanced cancer stage at diagnosis.

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