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A Prospective Study on Role of Serum TSH in Predicting Thyroid Malignancies

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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. In general population, thyroid nodules are very common with reported prevalence of 4-7% of adults. The challenge to clinicians is to identify the minority of thyroid nodules that harbour malignancy from the majority which can be managed conservatively. There are a number of well established of predictors of malignancy in thyroid nodules. More recently a few 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. *Aims And Objectives:* To evaluate the association between Serum Thyroid stimulating hormone (TSH) concentration and Thyroid cancer and also to assess whether Serum TSH levels are of value in predicting malignancy in patients with thyroid swellings. *Materials And Methods:* A both prospective and retrospective study was designed, including total of 90 cases of thyroid cancer. Age, sex, serum TSH concentration, nodule size and pathology were evaluated. The association between serum TSH concentrations and thyroid cancer was analysed. *Results:* In our study maximum number of thyroid cancer patients (79 out of 90) had Serum TSH concentrations ranging 1.71 mIU/L-5.5mIU/L i.e. within normal range but towards higher range. Even mean serum TSH concentrations in our study was found to be high in advanced stages of carcinoma had mean serum TSH concentration of 5.27 mIU/L. *Conclusion:* 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 signifies more aggressive and advanced cancer stage, at diagnosis.

Keywords: Malignancies; Thyroid stimulating hormone (TSH); Thyroid gland.

Introduction

Thyriod neoplasms are most common endocrine neoplasms in the body. Thyriod neoplasms constitute both benign and malignant lesions arising from thyroid gland.In India annual incidence accounts for 3.7 per 1 lakh population. Out of all malignancies thyroid malignancy accounts for less than 1 precent of cases. Greater than 75 percent of cases occur in women. Although less than 25 percent of cases occur in men they account for 45 percent mortality from thyroid malignancy. Thyroid malignancies are group of tumours with varied growth rates, therapautic response, varied histological response.

Glandular epithelium is the site from which most of benign tumours arise and are named as adenomas. They are true neoplasms and usually occur in middle age. Among benign lesions 80 percent occur in women [1,2].

Solitary nodules resected surgically malignancy is found in 15 to 30 percent in different series. Thyriod

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malignancy has known increase frequency with age and is rare in children.

Ninty to Ninty five thyroid malignancy are well differentiated which are arising from epithelium and have favourable prognosis [3].

A number of reports have identified baseline serum TSH concentrations as a predictor of the diagnosis of malignancy in patients with thyroid nodules . The first study, conducted by K. Boelaert *et al,* investigated 1500 euthyriod subjects presenting with thyroid enlargement and undergoing fine-needle aspiration biopsy. The risk of diagnosis of malignancy rose in parallel with seum TSH at presentation with significant increases evident in those with TSH>0.9 mIU/l compared with those with lower TSH concentrations [4]. For the first time, K. Boeleart *et al* identified serum TSH concentration as an independent predictor of the presence of thyriod malignancy in addition to patients age and gender as well as the goiter type evident on clinical examination . The lowest risk of malignancy was evident in patients with subclinical hyperthyroidism (TSH<0.4mIU/l), and the prevalence of thriod cancer was highest in those with subclinical hypothyroidism (TSH>5.5 mIU/l). Further analysis indicated significantly increased odds ratios for the presence of malignancy , even for TSH concentrations within the normal range [5]. These findings were subsequently confirmed by others.

Haymart *et al.* investigated 843 patients undergoing surgery and recorded the preoperative serum TSH concentration. The likelihood of malignancy was 16% when TSH was >0.06 mIU/l, 25% for TSH between 0.40 and 1.39mIU/l, 35% for TSH between1.40 and 4.99 mIU/l and 52% in those with TSH of 5.0 mIU/l or greater [6].

A further study by Polyzos *et al [7].* reported significantly increased adjusted odds ratios for the diagnosis of malignancy in those with TSH 1.5 -4.0 mIU/l when compared with those with lower serum TSH concentrations at presentation. Finally , a report of small series of 50 euthyriod patients undergoing thyriodectomy for a variety of reasons has confirmed increased risk of cancer diagnosis in subjects with serum serum TSH concentrations in the upper three quartiles of TSH values, compared with patients whose serum TSH was in the lower quartile. Furthermore, those who were subsequently diagnosed with thyroid cancer had lower serum concentrations of total tri-iodothyronine. Taken together, these findings suggest that serum TSH concentrations can be used as a diagnostic adjunct in the identification of high-risk patients who require further investigation and/or surgical intervention.

Haymart et al [8], demonstrated that higher preoperative serum TSH concentrations were not only associated with the incidence of differentiated thyroid cancer, but also with more advanced cancer stage at diagnosis. Mean serum TSH levels were significantly higher in those with stage III and IV disease when compared with those with more localised (stage I and II) disease. Staging were done based on TNM classification and staging. Further Fiore et al [9], confirm the finding of higher serum TSH in patients with T3–T4 tumour stage compared with those with stage T1–T2. Furthermore, median serum TSH concentrations were significantly higher in those with lymph node metastases compared with subjects without positive lymph nodes. This escalating risk of advanced disease further suggests that TSH is involved in the pathogenesis or progression of thyroid cancer.

Unique among all malignancies, the majority of staging systems for well-differentiated thyroid cancers includes age as one of the key prognostic factors. In iodine-replete healthy adult populations, such as the cohort investigated by, there is an increase in serum TSH with advancing age [10]. Further analysis of this cohort confirmed an association between advanced stage disease and higher serum TSH concentrations, independent of age. In addition, there was a significant correlation between higher TSH levels and extrathyroidal extension, but not with other factors associated with poor prognosis including age 45 years, tumour size 4 cm and presence of distant metastases. These findings raise the intriguing question whether higher serum TSH concentrations stimulate thyroid cancer invasion thereby facilitating extrathyroidal extension of disease [11].

Materials and Methods

This a prospective and retrospective study, done on subjects satisfying the inclusion and exclusion criteria from in-patients registry of Mysore Medical College And Research Institute, Mysore during study period of Januvary 2016 to December 2016.

Ninety patients of thyroid carcinoma without an overt thyroid dysfunction were included in our study. 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 age and sex, FNAC 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.

All cases of Thyroid cancer without overt thyroid dysfunction were included from the study. Patients in whom serum TSH levels were obtained while on thyroid hormone therapy, secondary malignancies in the thyroid, Thyroid lymphomas, Thyroiditis, Graves disease were excluded from the study.

Results

Maximum number of patients fell into 26-40 years age group 41 (45.56%) and 41-60 year age group 37 (41.11%). Maximum incidence of thyroid carcinoma was seen in female patients in 56 patients (62.22%). Preoperative diagnosis showed 73 (81.11%) solitary thyroid nodule and 17 (18.89%) multinodular goiter. Of 90 thyroid cancers, incidence of follicular carcinoma was 36(40%), 49 (54.44%) papillary carcinoma, 3 (3.33%) hurthle carcinoma and 2 (2.22%) anaplastic carcinoma [Table 1]. Maximum number of patients 79 (87.78%) of thyroid carcinoma had Serum TSH concentration in upper tertile of normal range (1.71- 5.5mIU/L) of which 63 (86.3%) solitary nodule of thyroid and 16 (94.12%) multinodular goiter [Table 2,3]. 34(94.44%) cases were follicular carcinoma, 43(87.76%) pappliary carcinoma and 2(6.67%) hurtle cell carcinoma had TSH concentration in the range of 1.71- 5.5mIU/L [Table 4]. Stage 1 and stage 2 had mean serum TSH concentration of 4.12mIU/L and 5.27mIU/L in Stage 3 and Stage 4 Thyroid cancers [Table 5].

Table 1: Incidence of Follicular and Papillary carcinoma

Carcinoma	Frequency	Percentage
Follicular Carcinoma	36	40
Papillary Carcinoma	49	54.44
Hurthle Carcinoma	3	3.33
Anaplastic Carcinoma	2	2.22
Total	90	100

Table 2: Serum TSH Concentrations

Serum TSH	Frequency	Percentage (%)
<0.91mIU/l	0	0
0.91-1.70 mIU/l	1	1.11
1.71- 5.5mIU/l	79	87.78
>5.51mIU/l	10	11.11

Table 3: Serum TSH concentration in Solitary nodule and Multinodular goiter

Serum TSH	STN (n=73)	MNG (n=17)	Total (n=90)
<0.91mIU/l	0	0	0
0.91-1.70 mIU/l	01 (1.36%)	0	1 (1.11%)
1.71- 5.5mIU/l	63 (86.3%)	16 (94.12%)	79 (87.78%)
>5.51mIU/l	9 (12.32%)	1 (5.88%)	10 (11.11%)

Table 4: Serum TSH Concentration in Papillary and Follicular carcinoma

Serum Tsh	Follicular (n=36)	Papillary (n=49)	Hurthle Cell (n=3)	Anaplastic (n=2)	Total (n=90)
<0.91mIU/l	0	0	0	0	0
0.91-1.70 mIU/l	0	1 (2.04%)	0	0	1 (1.11%)
1.71- 5.5mIU/l	34 (94.44%)	43(87.76%)	2 (66.67%)	0	79 (87.78%)
>5.51mIU/l	2 (5.56%)	5 (10.2%)	1 (33.33%)	2 (100%)	10 (11.11%)

Table 5: Serum TSH Concentration relation with stage of Thyroid carcinoma

Stage	Mean Serum TSH Concentration
Stage I, II	4.12 mIU/L
Stage III, IV	5.27 mIU/L

Discussion

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 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. 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 [15].

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 and by cases of tumor growth post-T4 withdrawal or recombinant TSH [16]. 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 [17]. 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 [18].

Considering serum TSH concentration as a 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 [19]. 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 [20].

In the study by Judy Jin et al [12]., the highest incidence of was seen in age group less than 30yr (32%). In our study incidence was high in age group 26- 40yr 41 (45.55%). The age incidence of our study matches with the above study. In the study by K. Boelaert et al [13], 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%,). In our study incidence of malignancy was more in solitary thyroid nodule(n= 90, 81.11%) when compared with multinodular goitre (n=90, 18.89%).

In the study by Judy Jin et al [12], the final histopathology report : Follicular carcinoma -12 (9%), Papillary carcinoma – 113 (87%) and Hurthle carcinoma- 5 (4%). In our study final histopathology report: Follicular carcinoma- 36 (40%), Papillary carcinoma– 49 (54.44%), Anaplastic carcinoma 2 (2.22%) and Hurthle carcinoma-3 (3.33%). In study done by K. Boelaert et al [13], 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 1.8–5.5mU/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 [7]., higher rates of malignancy were observed in patients with serum TSH concentration in upper tertile 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- 4.0mIU/L when compared to those with either TSH 0.4-0.8mIU/ L or TSH 0.9 -1.4 mIU/L .

In our study incidence of malignancy thyroid carcinoma was highest in patients with serum TSH

concentrations in range of 1.71-5.5mIU/l i.e., 79 (87.78%) of 90 patients correlating higher rate of malignancies in patients with TSH in upper tertile of normal range. Induvidually incidence of papillary carcinoma and follicular carcinoma was more in a range of serum TSH ranging from 1.71-5.5mIU/l i.e., in the range 43 (87.76%) of 49 papillary carcinomas and 34 (94.44%) of 36 follicular carcinomas.

In the study by M.R. Haymart et al [8], 204 of 239 patients had stage 1 and 2 thyroid cancer with mean serum TSH concentrations of 3.1 and 35 of 239 had stage 3 and 4 thyroid cancer with mean serum TSH level of 4.9mIU/l. In our study 74 of 90 patients had stage 1 and stage 2 with mean serum TSH concentration of 4.12mIU/l and 16 of 90 patients had stage 3 and stage 4 and mean serum TSH concentration of 5.27mIU/l. Our study results are in comparision with results of M.R.Haymart et al [8] study.

Conclusion

Thyroid malignancies have a varied clinical presentation. The commonest presentation being that of a solitary thyroid nodule. Though there are many predictors of thyroid malignancy, none of them can conclusively predict the nature of a thyroid nodule.

In our study we evaluated the utility of preoperative serum TSH levels as a predictor of malignancy and it did show a statistically significant correlation (P=<0.01) between higher TSH levels and malignant nodules. However this relationship between higher TSH levels was not seen in those presenting with no primary thyroid swelling and only cervical lymph node metastasis.

However, as all patients with a thyroid swelling undergo a thyroid function test it is important to pay special attention to the TSH values. TSH levels could be used as predictor in clinically suspect malignant thyroid swelling with a benign FNAC report. In such cases where TSH value is high, the FNAC can be relooked to confirm the diagnosis.

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