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Original Research Article

Correlation of serum thyroid stimulating hormone level to predict benign or malignant nature of thyroid swelling

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ABSTRACT

Background: Thyroid enlargement is a common clinical problem encountered in ENT practice, thyroid cancer, by contrast is less common. Several imaging modalities, FNAB and biomarkers are available but a simple clinical or biochemical diagnostic criterion is still lacking. Serum TSH is a well- established growth factor for thyroid nodules and thus can be used as a simple and reliable test to predict the risk of having a thyroid malignancy in a patient with thyroid swelling. Objectives were to correlate serum TSH level with benign or malignant nature of thyroid swelling and to evaluate the use of TSH level in predicting thyroid malignancy.
Methods: This was a prospective observational study conducted over a period of one year at department of otorhinolaryngology and head and neck surgery of a tertiary care center in Nepal involving a total of 61 patients with thyroid swelling who underwent thyroid surgery. Pre-operative serum TSH level was measured and correlated with final HPE diagnosis.
Results: The study included 61 patients of which 30 (49.2%) were malignant on histopathology report. The mean TSH level for benign cases was 1.97 mIU/l±0.99 and that for malignant cases was 3.85 mIU/l±1.20 (p=0.000), thus showing higher level of mean serum TSH in malignant group and also more in differentiated thyroid cancer.
Conclusions: Patients with higher range of TSH levels were more likely to have thyroid malignancy as compared to lower range even within normal value. Hence, serum TSH level can be a reliable marker to predict malignancy in thyroid swelling.

Keywords: Fine needle aspiration biopsy, Histopathological examination, Malignancy, Serum thyroid stimulating hormone, Thyroid swelling

INTRODUCTION

Thyroid swelling is a common clinical problem encountered in ENT practice. Thyroid nodule incidence increases with age, seen more in women, in people with iodine deficiency and after radiation exposure.[2] In 1968, the Framingham study estimated a 5% to 10% lifetime risk of developing a thyroid nodule [3] and the Whickham survey in the northeast of England reported a 15% prevalence of goiters on thyroid nodules.[4] Thyroid cancer, by contrast is less common, and the lifetime risk of developing thyroid cancer is estimated to be 0.84% for

women and 0.30% for men.[5] Regarding thyroid carcinomas, papillary and follicular thyroid cancers are together termed differentiated thyroid cancers and represent approximately 80% and 5-15% of thyroid cancers respectively. The remainder comprise of medullary (5-8%), anaplastic (2-10%) and other carcinomas (1-4%).[6]

Although several imaging modalities are available, fine needle aspiration biopsy (FNAB) remains the gold standard in the evaluation of patients presenting with thyroid enlargement as stated in recent guidelines published by the American Thyroid Association.[7] New diagnostic approaches based on thyroid cancer molecular biomarkers have recently been studied, and some are already introduced in clinical settings. Currently, the most successful panels testing for mutations in thyroid FNAB samples are those testing for BRAF and RAS point mutations and RET/PTC and PAX8/PPAPγ rearrangements, as well as TRK rearrangements.[8,9] Although the use of these molecular tools have been validated in some studies, these tests are expensive and their impact on patient management remains debatable.[10] Also, limitations in FNAB owing to scanty sample, vascularity of thyroid swelling, variation in sampling technique, skill of the performing expert, and the experience of pathologist interpreting the aspirate do pose a problem in definitive diagnosis.[11]

The role of TSH as a predictor of thyroid nodule malignancy has been evaluated in the last few years. Since, Boelaert in 2006 reported the relation between malignancy risk and serum TSH levels, many studies have been done with a common idea that there exists a direct relation between high serum TSH levels and risk of having a thyroid cancer. Well-differentiated thyroid cancers express TSH receptors.[12,13] 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.[14,15] Experimental animal models indicated that TSH stimulation is involved in the development of thyroid cancer and there are literature which have shown in mice and golden hamsters fed on a low-iodine diet that thyroid overstimulation by TSH leads to hyperplasia and eventually to the development of cancer.[16] 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.[17,18] Thus, the aim of the present study was to evaluate whether or not high TSH levels within the normal reference range can be used as a predictor of malignancy in nodular thyroid disease.

METHODS

Study design, location duration and population

Current study is a prospective study conducted at Department of Otorhinolaryngology and Head and neck surgery, Kathmandu medical college and teaching hospital, Sinamangal from January 2019 to December 2019 on Patient attending ENT OPD with thyroid swelling.

Sample size and sampling methods

Convenience sampling method was used. Sample size was calculated using following formula;

$$n = Z^2 2pq/d^2$$

Where n=sample size, z=1.96, p=prevalence of thyroid malignancy, q=1-p, e=allowable error, d= allowable error, thus sample size was calculated to be 61.

Inclusion criteria

Inclusion criteria were; All patients above 14 to 65 years, both gender and Patient who has been planned for thyroidectomy (any kind).

Exclusion criteria

Exclusion criteria were; Patient who do not give consent for the study, Patient with overt thyroid dysfunction, Patients on thyroid hormone therapy and Patient not willing to undergo surgery.

Consecutive sampling was done and informed written consent was taken. Detailed history and clinical examination of thyroid swelling was done. Thyroid function test, ultrasonography and fine needle aspiration cytology were sent as an initial investigations and reports collected pre-operatively.

Chemiluminescence immunoassay technique was used to measure the TSH level. As per reference of the hospital, the range of normal TSH was 0.30-4.50 mIU/ml. Pre anesthetic checkup was done prior to surgery. Total or Hemi thyroidectomy under general anesthesia was performed accordingly by the consultant ENT-HNS surgeons under standard protocol. Post-surgery specimen was sent for histopathological evaluation (HPE). Gross and microscopic examination was done and reporting done by consultant pathologists.

The final diagnostic outcome was tabulated as the presence of benign or malignant pathology on the thyroid specimen. Final diagnosis (presence of benign or malignant nature of thyroid specimen) was co-related with the pre-operative serum TSH level.

Statistical analysis

The data collected and entered in the Microsoft Excel was exported to and analyzed in SPSS Version 23. Percentage, mean and standard deviation of all was calculated. Statistical tool used was independent ‘t’ test.

RESULTS

A total number of 61 patients were enrolled in this study with mean age ±SD being 39.87±11.34 years. The minimum age of patient was 20 years and the maximum being 60 years.

Out of the total patients, 52 (85.2%) were female and only 9 (14.8%) were male. Regarding sex distribution in two groups, most of the cases were female. Out of total 52 females 27 (44.3%) were benign and remaining 25 (41.0%) were from malignant group. Remaining nine male patients had four (6.6%) in benign and five (8.2%) in malignant group.

Pre-operative TSH level

Mean pre-operative TSH level obtained was found to be 2.89 mIU/l±1.44 (Table 1).

Table 1: Mean pre-operative TSH level.

Parameters	N	Mean	SD
Pre operative TSH level (mIU/l)	61	2.89	1.44

Ultrasonographic impression of thyroid nodule

Pre-operative ultrasonography finding showed that most cases were solitary nodule i.e. 49 (80.3%) of total cases and remaining 12 (19.7%) presented with multinodular goiter.

On final HPE diagnosis, 30 (49.2%) of total solitary nodule came out to be malignant whereas all 12 (19.7%) cases of multinodular goiter came to be benign. (Table 2). So, majority of cases with solitary nodule were of malignant nature and that of multinodular goiter were benign.

Table 2: USG Impression of thyroid nodule:

Benign vs. malignancy		Ultrasonography		Total
		Multinodular Goiter	Solitary Nodule	
Benign	N	12	19	31
	%	19.7	31.1	50.8
Malignancy	N	0	30	30
	%	0.0	49.2	49.2
Total	N	12	49	61
	%	19.7	80.3	100

Pre-operative FNAC

Pre-operative FNAC report showed out of total 61 cases, maximum number of cases was that of colloid goiter which was 30 (49.2%) followed by papillary carcinoma i.e. 19 (31.1%). 10 (16.4%) cases were that of follicular neoplasm and one each (1.6%) of medullary carcinoma and adenomatous nodule (Table 3).

Table 3: Preoperative FNAC report

Parameters	N	%
Colloid goiter	30	49.2
Papillary carcinoma	19	31.1
Follicular neoplasm	10	16.4
Medullary carcinoma	1	1.6
Adenomatoid nodule	1	1.6
Total	61	100.0

Histopathological examination

Colloid goiter was with maximum number 24 (39.3%) of cases followed by Papillary carcinoma with 21 (34.4%) cases, NIFTP with five (8.2%) cases, Hurthle cell adenoma with four (6.6%) cases, follicular adenoma with three (4.9%) cases, follicular carcinoma with two (3.3%) cases and Medullary carcinoma and Hurthle cell Carcinoma with one (1.6%) each case (Figure 1).

On the basis of post-operative histopathological (HPE) report, final diagnosis was made. There were total 40 benign cases on FNAC, out of which 11 (36.7%) came out to be malignant on HPE reports.

Out of 21 malignant cases on FNAC, two (6.5%) came out to be benign on final HPE reports (Figure 1).

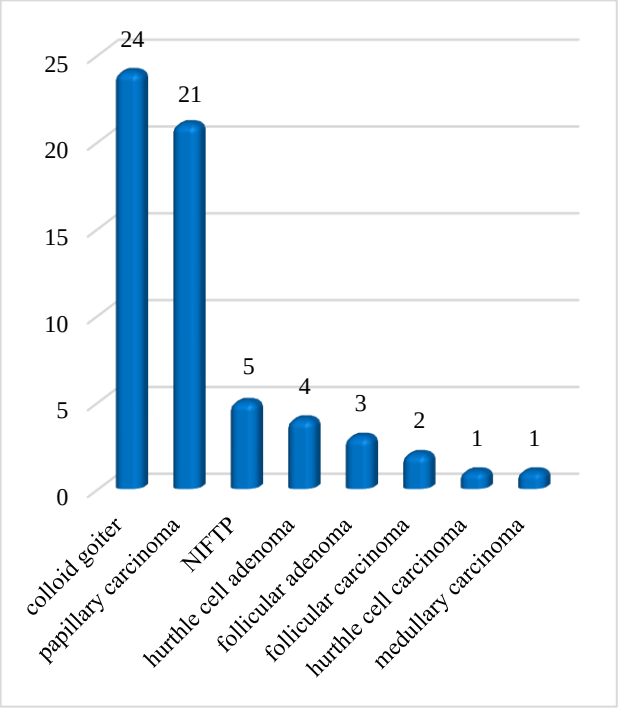

Figure 1: Post-operative histopathological reports.

Pre-operative TSH level and histopathology reports

Serum pre-operative TSH level was divided into 6 equal parts within the normal range. In this study, there were more benign cases when the TSH level was in lower

range compared to malignant cases when the TSH level was in higher range.

For example; in the range 1.14-1.97, there were 14 (23.0%) benign cases and only three (4.9%) malignant cases while in the range 3.66-4.50, all 13 (21.3%) cases were malignant (Figure 2).

Pre-operative TSH level (mIU/l) and post-operative histopathological examination (malignant cases)

Most of the malignant cases had pre-operative TSH level in higher range within the normal range. In the range 1.14-1.97, there were only three malignant cases all of which being NIFTP.

Table 4: Pre-operative TSH level (mIU/l) and post-operative histopathological examination (malignant cases).

Pre operative TSH level (mIU/l)		Postoperative Histopathological Examination					Total
		Papillary carcinoma	Medullary carcinoma	NIFTP	Follicular carcinoma	Hurthle cell carcinoma	
1.14-1.97	N	0	0	3	0	0	3
	%	0.0	0.0	9.7	0.0	0.0	9.7
1.98-2.81	N	1	0	0	0	0	1
	%	3.2	0.0	0.0	0.0	0.0	3.2
2.82-3.65	N	8	0	0	0	0	8
	%	25.8	0.0	0.0	0.0	0.0	25.8
3.66-4.50	N	9	0	2	2	0	13
	%	29.0	0.0	6.5	6.5	0.0	41.9
>4.50	N	4	1	0	0	1	6
	%	12.9	3.2	0.0	0.0	3.2	19.4
Total	N	22	1	5	2	1	31
	%	71.0	3.2	16.1	6.5	3.2	100.0

In the range 1.98-2.81, only one case of papillary carcinoma was present. Eight cases of papillary carcinoma had TSH level in the range 2.82-3.65; while in the range 3.66-4.50, there were nine cases of Papillary carcinoma, two of NIFTP and two of follicular carcinoma. Finally, four cases of Papillary carcinoma, one each of Medullary and Hurthle Cell carcinoma had TSH level >4.50 (Table 4).

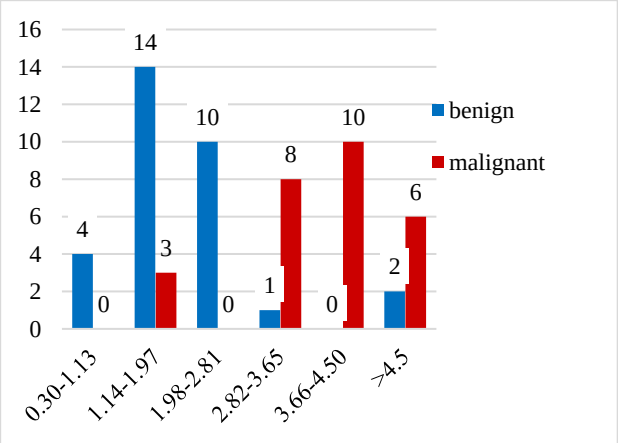

Figure 2: Pre-operative TSH level and HPE reports.

Using independent 't' test, mean TSH of benign and malignant cases was calculated. Here, mean TSH level for benign cases was 1.97 mIU/l±0.99 and that of malignant cases was 3.85 mIU/l±1.20 which was statistically significant ($p<0.05$). Thus, the serum TSH level has been seen to be a reliable marker to predict malignancy in thyroid swelling which is seen here with significant p value.

DISCUSSION

TSH levels are significantly higher in patients with thyroid malignancy than those in subjects drawn from the general population. We found that a higher TSH concentration within the normal range was an independent predictor of the presence of thyroid malignancy regardless of age and gender. TSH stimulates the production and release of thyroid hormones and promotes thyroid growth.[20] Thyrocytes in benign nodules and DTC express TSH receptors, and TSH is the main growth factor for thyroid through interactions with TSH receptors.[13] Administering exogenous thyroid hormone at supraphysiologic doses suppresses the secretion of TSH. Suppressed TSH inhibits the growth and development of nodules and improves overall survival in high-risk patients with DTC.[13,21-23] In this study, we were able to show that higher serum TSH levels correlate with a higher risk of malignancy in patients with thyroid swelling. As serum TSH increased, the likelihood of malignancy rose. Using independent 't' test the mean value of TSH for benign cases was 1.97 mIU/l±0.99 and that of malignant cases was 3.85 mIU/l±1.20 ($p=0.000$). Haymart et al did a cohort study in 2009 and found that mean TSH was significantly higher in cancer patients regardless of age. Furthermore, Haymart et al have identified a relationship between higher serum TSH levels and extrathyroidal tumor extension and suggest

that this is the explanation for the association of higher serum TSH levels and more advanced stage of disease.[24]

Boelaert et al demonstrated for the first time that the risk of diagnosis of malignancy rises in parallel with the serum TSH concentration at presentation, and further analysis indicated significantly increased odds ratios for the presence of malignancy in patients with TSH greater than 1.8 mU/l after adjustment for patients' gender, age, and goiter type.[25] In 2010, Jin et al published an article mentioning TSH level is higher in the malignant group (5.5 mIU/ml vs. 1.4 mIU/ml, $p<0.0001$).[19] Mussa et al published retrospective analysis of serum TSH concentrations which showed serum TSH concentration was significantly higher in patients with thyroid cancer compared with those with benign nodules (3.23±1.59 mU/l vs. 1.64±0.99 mU/l; $p<0.001$).[26] Hamdi et al studied that the mean TSH is higher in the malignant group (2.07 vs. 1.07, $p=0.02$).[27] Chandrika et al and Golbert et al told that the mean TSH value is higher in malignancy when compared with benign lesions.[28,29] Recently, a meta-analysis study has revalidated that elevated preoperative TSH levels are associated with increased risk of thyroid cancer. Twenty-eight studies were analyzed in the meta-analysis, in which a total of 42032 control subjects and 5786 thyroid cancer cases were included. All the studies in the meta-analysis determined the risk of DTC in patients with nodular thyroid diseases.[30]

As seen from above studies, this study is comparable in terms of relations of mean TSH in malignant thyroid nodule compared to benign nodule. This shows that high TSH level is associated with thyroid malignancy. Additional analysis using TSH levels as a categorical variable show that the prevalence of malignancy was higher in patients with TSH levels in upper range as compared with patients with lower TSH levels. For example; in the range 1.14-1.97, there were 14 (23.0%) benign cases and only 3 (4.9 %) malignant cases while in the range 3.66-4.50, all 13 (21.3%) cases were malignant. This means with increasing value of serum TSH level there is increased chance of having thyroid cancer. This is in accordance with study done by Boelart et al in 2006 where he concluded that there is significant increased adjusted odds ratios for the diagnosis of malignancy in subjects with high serum TSH.[25] Prasad et al in 2017 did a case control study in a tertiary care center and significant association was observed between TSH levels and diagnosis of thyroid lesions. TSH was raised (>4 mIU/l) in 46.6% of malignant nodules and 15 % of benign nodules.[31] Based on the data provided by this study, it is very practical to state that higher serum TSH level is associated with higher risk of malignancy. But despite the consistent association between higher TSH levels and malignant nodules shown in most series, including this one, an optimal TSH cut-off value for predicting the risk of cancer has not been yet identified. Thus, the result presented here might have important clinical implications, since it indicates that the TSH levels may help in the diagnostic strategy, in conjunction with clinical, ultrasonographic and cytological features. However, serum TSH should not be used for diagnostic decision making in isolation.

CONCLUSION

Higher serum TSH levels are associated with an increased risk of thyroid malignancy in patients presenting with thyroid nodules. This study demonstrated that mean serum TSH value of a malignant nodule is higher than that of a benign nodule. Also, the prevalence of malignancy increases with increasing level of serum TSH range. Thus, serum TSH level has been seen to be a reliable adjunct on predicting malignancy in thyroid swelling.

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