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Original Article

Biochemistry Section

Evaluation of Thyroid Swellings for Incidence of Thyroid Cancer and their Association with Serum Thyroid Stimulating Hormone and Triglyceride Levels: A Cross-sectional Study

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ABSTRACT

Introduction: Earlier, several studies have been evaluated the role of Thyroid Stimulating Hormone (TSH) as a predictor of thyroid cancer in patients presenting with thyroid swelling but it remains unclear.

Aim: To evaluate the role of TSH in non neoplastic tumours and neoplastic tumours and its association with various types of thyroid neoplastic tumours.

Materials and Methods: In this retrospective cross-sectional study, the records of 138 patients from March 2017 to February 2019 with thyroid swelling were evaluated and analysis was done in October 2020. Examination of following parameters like age, sex, Free Triiodothyronine (FT3), Free Tetraiodothyronine (FT4), Thyroid Stimulating Hormone (TSH), Total Cholesterol (TC), Triglycerides (TGL), Low Density Lipoprotein (LDL) and High Density Lipoprotein (HDL) cholesterol were done. All the patients were divided into two groups viz., neoplastic and non neoplastic on the basis of Fine Needle Aspiration Cytology (FNAC) diagnosis. One-way ANOVA and Student's t-test were used for the analysis of thyroid tumour patients. The p-value of <0.05 was considered to be significant.

Results: Out of 138 cases identified, 38 cases (27.5%) were between 10-30 years of age, 90 cases (65.2%) between 31-50 years and 10 cases (7.3%) between 51-70 years of age. The incidence of thyroid pathology was significantly high in patients with age >30 years of age as compared to ≤30 years of age patients (27.5% vs 72.5%, Υ^2=55.7, p-value <0.05). The incidence of thyroid tumours was high in females than in males and is statistically significant (20.3% vs 79.7%, Υ^2=97.44, p-value <0.05). Out of 138 patients, euthyroid was observed in 71 patients, overt hypothyroidism in 37, Subclinical Hypothyroidism (SCH) in 14, overt hyperthyroidism in 11 and subclinical hyperthyroidism in four patients. Hypothyroidism was found in 50% of neoplastic tumour patients which is significantly high as compared to non neoplastic tumour patients. Significantly higher levels of TSH were noted in neoplastic group as compared to non neoplastic group (p-value <0.05).

Conclusion: The high serum concentrations of TSH in patients with thyroid swellings should be evaluated properly for the early diagnosis of thyroid cancers. The data from our study provided the evidence for a possible association of TSH, TGL with thyroid cancer.

Keywords: Hypothyroid, Neoplastic tumours, Non neoplastic tumours

INTRODUCTION

Most of the thyroid swellings are non neoplastic and do not require surgical treatment. The incidence of thyroid swelling was found to be 75.84% in the age group of 20-40 years with male to female ratio of 1:4 [1]. Thyroid nodules and goitre are the most common thyroid disorders and are primarily due to interaction between genetic, environmental or endogenous factors. The prevalence of these nodules ranges from 19% to 67%, however 4%-7% are palpable [2]. Majority of nodules and goitre have no clinical symptoms but both these disorders can be associated with endocrine dysregulation, autoimmune thyroid condition, impaired body composition or various metabolic abnormalities [3].

The components of metabolic syndrome such as obesity, Insulin Resistance (IR), hypertension, dyslipidemia and impaired glucose metabolism are associated with structural abnormality of thyroid that may leads to increased thyroid volume and nodular prevalence [4]. In addition, the recent studies also accentuated the importance of hyperinsulinemia and IR in the proliferation of thyroid cells [5,6].

Thyroid function tests aids in differentiating various types of thyroid dysfunction. TSH is the first line thyroid function test to assess the thyroid status of an individual in any clinical condition [7]. Although the advancement of imaging techniques are available, FNAC remains the gold standard surgical technique in the evaluation of the thyroid swellings [8], as it bridges the gap between clinical findings and laboratory tests for diagnosis and thereby reduces the surgical intervention. [9]. In addition, the accuracy rate of FNAC exceeds 92% [10]. Therefore, the use of FNAC in association with thyroid profile helps to assess the nature and stage of the disease and adaptation of treatment as well.

Chronic over stimulation of TSH causes thyroid follicular cells to proliferate but in iodine deficient animals this proliferation increases by 5-30 fold [11]. So, it results in chromosomal changes with increased number of aneuploid cells [12]. By keeping in view that TSH has a role in the development of thyroid cancer, the present retrospective study was aimed to know the incidence of thyroid tumours, and to evaluate the association of TSH with various types of thyroid tumours.

MATERIALS AND METHODS

In this retrospective cross-sectional study, records of 138 patients who have visited Ear, Nose, Throat (ENT) and General Surgery Departments of Anil Neerukonda Hospital, NRI Institute of Medical Sciences for thyroid swelling evaluation from March 2017 to February 2019 with thyroid swelling were evaluated and analysis was done in October 2020. Since, the analysis was based on the pre-existing data available with hospital information system, informed consent was not taken from the subjects. The study was approved by the

Institutional Ethics Committee (Ref No: NRIIMS/IEC/07/2018 dt 03/03/2018) of NRI Institute of Medical Sciences.

Demographic data and biochemical results such as thyroid profile (measured by fully automated electro-chemiluminescent immunoassay using commercially available kits from bioMerieux SA with Vidas analyser) and lipid profile (measured by fully automated biochemistry analyser) of all the patients were reviewed. Thyroid dysfunction {overt hypothyroidism, Subclinical Hypothyroid (SCH)}, hyperthyroidism and subclinical hyperthyroidism was defined as per the standard cut-offs of Free Triiodothyronine (FT3), Free Tetraiodothyronine (FT4) and TSH in different age groups of manufacturer's manuals. Data was also collected for FNAC findings for all these patients and analysed retrospectively. All the patients with known thyroid disorders and patients undergoing thyroid medication were excluded from the study.

STATISTICAL ANALYSIS

The difference in the levels of biochemical parameters such as FT4, FT3, TSH, TC, Low Density Lipoprotein (LDL) cholesterol, High Density Lipoprotein (HDL) cholesterol and TGL among non neoplastic and neoplastic thyroid tumour patients were analysed by Student's t-test whereas the significance of TSH between neoplastic and non neoplastic tumours were analysed by one-way ANOVA and the p-value <0.05 was considered to be significant.

RESULTS

The present retrospective study comprised of 138 patients with thyroid swelling and age, gender distribution of thyroid cases was depicted in [Table/Fig-1]. Out of 138 cases identified 38 cases (27.5%) between 10-30 years of age, 90 cases (65.2%) between 31-50 years and 10 cases (7.3%) between 51-70 years of age. The incidence of thyroid pathology was significantly high in patients with age >30 years of age compared to ≤30 years of age patients (27.5% vs 72.5%, Υ^2=55.7, p<0.05). The most common age group was 31-40 years in both males and females. Among 138 patients, males were 28 (20.3%) whereas females were found to be 110 (79.7%). The male to female ratio was 1:4. The incidence of thyroid tumours was high in females than in males and is statistically significant (20.3% vs 79.7%, Υ^2=97.44, p<0.05).

Age (in years)	Male n=28 (%)	Female n=110 (%)
10-20	1 (3.6)	3 (2.7)
21-30	2 (7.1)	32 (29.1)
31-40	12 (42.9)	50 (45.5)
41-50	5 (17.9)	23 (20.9)
51-60	7 (25)	1 (0.9)
61-70	1 (3.5)	1 (0.9)

[Table/Fig-1]: Age and sex wise distribution of cases (n=138).

Distribution of type of tumours based on FNAC diagnosis was shown in [Table/Fig-2]. Out of 138 patients studied, neoplastic and non neoplastic tumours were present in 30 and 108 patients, respectively. In neoplastic tumours, papillary tumours are more commonly occurred (63.3%) and ranked top followed by follicular tumours (30%).

Type of tumours	No. of cases
Non neoplastic	**(n=108) (%)**
Nodular goitre	91 (84.3)
Lymphocytic	13 (12.0)
Thyroiditis	4 (3.7)
Neoplastic	**(n=30) (%)**
Papillary	19 (63.3)
Follicular	9 (30)
Anaplastic	1 (3.3)
Follicular adenoma	1 (3.3)

[Table/Fig-2]: Distribution of type of tumour based on FNAC diagnosis.

Biochemical characteristics of study population were presented in [Table/Fig-3]. Significantly high levels of serum TSH were seen in neoplastic tumour patients as compared to non neoplastic tumour patients (p-value <0.05). Similarly, significant difference was found in the serum levels of TC and HDL cholesterol between these two groups however no significance was observed in serum LDL cholesterol, FT3 and FT4 levels between these groups. Serum triglyceride and TC levels were also found to be significantly high in neoplastic tumour group whereas HDL cholesterol was significantly low when compared to non neoplastic tumour patients (p-value <0.05). Thyroid status of neoplastic vs non neoplastic tumours was depicted in [Table/Fig-4].

Biochemical parameter	Non neoplastic n=108 (Mean±SD)	Neoplastic n=30 (Mean±SD)	Student's t-test p-value
FT4 (ng/dL)	1.05±0.81	1.14±0.67	0.57
FT3 (pg/mL)	4.16±2.18	4.22±4.54	0.91
TSH (µIU/mL)	3.42±1.91	8.16±5.32	<0.001*
TC (mg/dL)	154±13.9	200±9.18	<0.001*
LDL cholesterol	116±27.8	118±28.2	0.72
HDL cholesterol	37.2±2.26	35±1.24	<0.001*
TGL (mg/dL)	119±14.4	194±10.9	<0.001*

[Table/Fig-3]: Biochemical characteristics of non neoplastic vs neoplastic tumour patients.
FT4: Free T4; FT3: Free T3; TSH: Thyroid stimulating hormone; TC: Total cholesterol; LDL: Low density lipoprotein; HDL: High density lipoprotein; TGL: Triglycerides; p<0.05 statistically significant

Thyroid status	Non neoplastic n=108 (%)	Neoplastic n=30 (%)
Euthyroid	62 (57.4)	9 (30)
Overt hypothyroid	22 (20.4)	15 (50)
Subclinical hypothyroid	10 (9.3)	4 (13.3)
Overt hyperthyroid	11 (10.2)	0 (0)
Subclinical hyperthyroid	3 (2.8)	1 (3.3)

[Table/Fig-4]: Thyroid status of neoplastic vs non neoplastic tumour patients.

Out of 138 patients, euthyroid was observed in 71 patients, overt hypothyroidism in 37, SCH in 14, overt hyperthyroidism in 11 and subclinical hyperthyroidism in 4 patients. Among 108 non neoplastic tumour patients, euthyroid was seen in 62 patients (57.4%), followed by 22 hypothyroid patients (20.4%). Hypothyroidism was found in 50% of neoplastic tumour patients which is significantly high as compared to non neoplastic tumour patients. Serum TSH levels of various tumour types of both neoplastic and non neoplastic were depicted in [Table/Fig-5]. Significantly higher levels of TSH were noted in neoplastic group as compared to non neoplastic group (p-value <0.05).

	Neoplastic tumours		Non neoplastic tumours			
	Papillary (n=19)	Follicular (n=9)	Nodular goitre (n=91)	Lymphocytic (n=13)	Thyroiditis (n=4)	ANOVA p-value
TSH	8.09±5.69	8.32±4.76	1.88±1.4	2.87±2.39	4.56±1.98	<0.001* <0.001**

[Table/Fig-5]: Serum TSH status in various tumour types and its significance.
p<0.05* statistically significant; <0.001*: Papillary vs non neoplastic tumours; <0.001**: Follicular vs non neoplastic tumours

DISCUSSION

Thyroid gland tumours are the most common endocrine neoplasms in India seen in 8.5% of the population [13]. The prevalence of thyroid nodular disease ranges between 26%-67%, out of which 8%-15% of all thyroid nodules are carcinomas [14]. Thyroid nodules are more frequently seen in women particularly the elderly, individuals with a history of exposure to ionising radiation, and iodine deficient areas [15]. In the present retrospective study, the incidence of thyroid tumours in females was four times higher than in males suggesting the females were more vulnerable to thyroid pathology due to hormonal factors although the causes are unclear. The literature also

suggests that the biological changes occurring during pregnancy may increase the risk of thyroid carcinoma. Our findings were in association with Afroze N et al., and other studies [16,17] where similar results were declared and their incidence increased as age advanced. In this retrospective study, patients with thyroid swelling were in the age group of 10-70 years with a median age of 37.8 years. This age group distribution of cases was comparable with Jose RM et al., where similar observations were found [18].

According to research data, the high prevalence of thyroid nodules is widely observed in iodine deficient subjects [19] and is due to the higher levels of TSH which is an adaptation process to iodine deficiency [20]. In this retrospective study, the diagnosis was made by FNAC findings had shown that among 138 cases of thyroid swellings, 21.7% were found to be neoplastic and rest 78.3% were non neoplastic tumours. Out of 30 neoplastic tumours, papillary carcinoma was identified in 19 cases (63.3%) followed by follicular in 9 cases (30%), anaplastic in 1 (3.3%) and follicular adenoma in 1 (3.3%) cases. Increased incidence of papillary carcinoma has been observed in parallel with increases in iodine intake [21]. Infact, high incidence of papillary thyroid carcinoma over follicular carcinoma has been identified in areas where iodine forfeit is observed for the prophylaxis of goitre [22,23]. This distribution of cases was in accordance with earlier study where papillary carcinoma was more common type [24]. However, authors did not have clear data related to iodine supplementation in our patients.

Out of 108 non neoplastic thyroid tumour patients, euthyroid was found in 57.4% of cases, hypothyroidism in 20.4% and overt hyperthyroidism in 10.2% of patients. Similarly, Kumar V et al., also noticed similar results where euthyroid was found to be 50%, overt hypothyroid 38% and hyperthyroidism 12% in thyroid tumour patients [25]. In addition, Fenn AS et al., also found similar results in their study [26]. In non neoplastic patients, euthyroid was noticed in 57.4% cases whereas in neoplastic group 30% of them were euthyroid. However, overt hypothyroidism was found in 50% of neoplastic cases and 20.4% of non neoplastic cases. Our results were in agreement with earlier studies where similar results were obtained [25].

In most of the thyroid cancers, the thyroid nodule and goitre precede its development [27]. It is evident from animal studies that the chronic stimulation of TSH causes thyroid tumours. It is observed that the role of TSH as a predictor of thyroid malignancy in several studies [28] but at the same time several others reported the conflicting results [29,30]. TSH together with growth factors contribute significantly for the development of thyroid cancer by stimulating second messenger pathways and ultimately resulting in a modulation of thyroidal gene expression [31]. This is evidenced by suppressive doses of levothyroxine [32] or by recombinant TSH [33] improved the thyroid cancer successfully. In this retrospective study, elevated serum TSH levels were found in neoplastic tumours of papillary and follicular type compared to non neoplastic tumours suggesting the role of TSH in the pathogenesis of thyroid cancer. Earlier, Haymart MR et al., also stated that higher TSH levels significantly correlated not only with increased risk and frequency of malignancy but also with a more advanced stage of thyroid cancer [34] suggesting the overexpression of TSH receptor is probably involved in the pathogenesis of thyroid cancer and deregulation of genes involved in thyroid hormone biosynthesis. In addition, higher levels of TSH were noticed in female patients with thyroid swelling indicating that female group is more vulnerable due to hormonal factors involved.

TGL has a role in the pathogenesis of lung, thyroid, prostate and gynaecological cancers [35]. Many of the studies have emphasised that the hypoactivity of thyroid can cause hypertriglyceridemia by interfering with cholesterol production [36]. In the present retrospective study, significantly high levels of serum TGL were found in thyroid neoplastic tumour patients compared to non neoplastic thyroid tumour patients suggesting the underactivity of thyroid in neoplastic tumours.

Limitation(s)

Limitation of the study was less sample size, less clinical data and retrospective study. Moreover, anthropometric measurements and iodine levels were not considered in the study. More extensive prospective studies for long duration are essential to establish a firm conclusion on the association between TSH and thyroid tumours.

CONCLUSION(S)

The high serum concentrations of TSH in patients with thyroid swellings should be evaluated properly for the early diagnosis of thyroid cancers. The data from our study provided the evidence for a possible association of TSH, TGL with thyroid cancer. More such studies are required to explore underlying mechanisms for the association between TSH, TGL and thyroid cancer.

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