

Original Research Article

Serum thyroglobulin level in newly detected thyrotoxicosis and its role in differential diagnosis of thyrotoxicosis

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ABSTRACT

Background: Elevated serum thyroglobulin (Tg) level is commonly observed in various forms of thyrotoxicosis; the levels vary according to different etiologies. This study aimed at identifying the value of serum Tg level in the differential diagnosis of common etiologies of thyrotoxicosis.

Methods: This cross-sectional study was conducted at the endocrine outpatient department of a tertiary hospital in Bangladesh from March 2015 to May 2017. In this study, 200 subjects with newly detected untreated thyrotoxicosis were evaluated. Serum Tg was assayed by chemiluminescent immunometric assay.

Results: Serum Tg level was raised in 48% of subjects. Subjects aged ≥ 40 years, and those having a family history of thyroid disorders had relatively higher thyroglobulin levels. The frequency of subjects with an elevated Tg was highest in subacute thyroiditis (89.5%) followed by toxic nodular goiter (77.3%) and Graves' disease (32.9%); the difference in the frequencies was statistically significant ($p < 0.001$). Median Tg was highest in the subjects with subacute thyroiditis (132.6 ng/ml) followed by toxic nodular goiter (99.55 ng/ml); those with Graves' disease had the lowest Tg level (12.5 ng/ml); the differences in median Tg levels across the three groups were also statistically significant ($p < 0.001$).

Conclusions: Serum thyroglobulin level may be useful for the etiological diagnosis of thyrotoxicosis.

Keywords: Thyroglobulin; Thyrotoxicosis; Graves' disease; Subacute thyroiditis; Toxic nodular goiter

INTRODUCTION

The term "thyrotoxicosis" refers to the clinical state resulting from inappropriately high thyroid hormone action in the target tissues, generally due to inappropriately high tissue thyroid hormone levels. "Hyperthyroidism" is the form of thyrotoxicosis due to inappropriately high synthesis and secretion of thyroid hormone(s) by the thyroid gland. The two terms are often used

interchangeably.¹ The prevalence of overt hyperthyroidism ranges from 0.2% to 1.3% in iodine-sufficient parts of the world.² Graves' disease (GD), toxic multinodular goiter (TMNG), toxic adenoma (TA), and various forms of thyroiditis are the most common causes of thyrotoxicosis.^{1,2} As treatment plans are different for these causes of thyrotoxicosis, the etiological diagnosis should be established before starting treatment.¹ The initial evaluation for differentiation of common etiologies of

thyrotoxicosis include ultrasonography (USG) of thyroid with measurement of thyroidal blood flow, determination of the radioactive iodine uptake (RAIU), and measurement of thyrotropin receptor autoantibody (TRAb); a ^{123}I or $^{99\text{m}}\text{Tc}$ pertechnetate scan should be obtained when the clinical presentation suggests a TA or TMNG.¹

Serum Tg level alters in almost all thyroid disorders, but serum Tg is primarily used as a tumor marker in the follow-up of differentiated thyroid carcinoma.³⁻⁵ Few researchers have evaluated the use of serum Tg in the differential diagnosis of thyrotoxicosis, especially factitious thyrotoxicosis and subacute thyroiditis.⁵⁻⁸ Patients with active GD, TMNG, and TA also have been found to have elevated levels of Tg.⁸

Except for ultrasonographic evaluation of the thyroid gland, other tests used for differentiation of etiology of thyrotoxicosis are not readily available, especially in developing countries, those may also be time-consuming, and some have the risk of radiation exposure. Measurements of serum Tg is simple, inexpensive, and presents no risk of radiation exposure.⁶ We conducted this study to identify the role of serum Tg level in the differential diagnosis of common etiologies of thyrotoxicosis.

METHODS

This cross-sectional study was conducted at the endocrine outpatient department (OPD) of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, from March 2015 to May 2017. The study protocol was approved by the Institutional Review Board of the University. Newly diagnosed adults (≥ 18 years) with various forms of hyperthyroidism attending the OPD were considered the study population, and samples were collected consecutively by purposive sampling technique; informed written consent was obtained from all.

In this study, the diagnosis of thyrotoxicosis and its differential diagnosis into its four major etiology, namely GD, TMNG, TA, and subacute thyroiditis was made according to the criteria set by the American Thyroid Association based on clinical features, assessment of thyroid function by measurement of thyroid-stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine (FT3) levels, USG of the thyroid gland, RAIU test, and $^{99\text{m}}\text{Tc}$ pertechnetate scan.¹ Patients with thyroid malignancy, pregnant and lactating women, psychological impairment and critically ill patient, thyrotoxicosis on treatment, taking drugs interfering with thyroid metabolism including L-thyroxine, Lithium, Amiodarone and patient with significant comorbidities were excluded. Patients who gave informed written consent were interviewed and examined for relevant demographic and clinical information. A semi-structured data collection sheet was used to collect and record data, which included general information on demographic characteristics, history of medical illness, previous history

of thyroid disease, family history of thyroid disease, type and grade of goiter, etc. Goiter grading was done according to the classification system described by the World Health Organization (WHO).⁹ Within the study period, 200 patients with hyperthyroidism were selected consecutively for final analysis.

Laboratory assessment

Analysis of serum TSH, FT4, FT3, and Tg was done in the Immunology Laboratory of the institute by using the chemiluminescent sequential immunometric assay IMMULITE® 2000 immunoassay system (Diagnostic Products Corporation, Siemens, Germany). Tg level was interpreted according to the reference range of the corresponding laboratory (normal range: 0-55 ng/ml); serum Tg > 55 ng/ml was considered as elevated Tg. USG of the thyroid gland, RAIU test, and $^{99\text{m}}\text{Tc}$ pertechnetate scan were performed in the National Institute of Nuclear Medicine and Allied Sciences (NINMAS) located at the university campus.

Ethical consideration

The study protocol was approved by the Institutional Review Board of the University. Informed written consent was taken from each of the patients before taking any interviews after describing the study's purpose and methods, the confidentiality of the interviews, risks, and benefits of participating in the study. All information was collected confidentially with complete respect to the patient with and without any force or pressure.

Statistical analysis

Data were analyzed using the Statistical Product and Service Solutions version 23.0 software (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY: IBM Corp.) and STATA version 16. The categorical variables were represented as percentages and measurable variables as the median and interquartile range (IQR). Nonparametric tests and Chi-square tests were performed to compare the variables between different groups as appropriate. Kernel density plots were used to express the values of serum Tg in different categories of hyperthyroidism. P value ≤ 0.05 was considered statistically significant.

RESULTS

The demographic and clinical characteristics of the study population and the comparison of those variables between subjects with normal thyroglobulin level and high thyroglobulin level are shown in Table 1. The median Tg level was higher, and the number of subjects with elevated Tg was higher in subjects with age > 40 years, those having a family history of thyroid diseases, and those with nodular goiter compared to their counterparts. Tg levels and elevated Tg frequency were similar across gender, different goiter grades, and ophthalmopathy status.

Table 1: Serum Tg across the subcategories of different variables.

Variables	Sub-categories	N	Tg level (ng/ml) Median (IQR)	P	Tg status		P
					Normal N (%)	Elevated N (%)	
Age (years)	≤ 40	110	19.4 (3.5-105.9)	0.003	67 (60.9)	43 (39.1)	0.005
	> 40	90	74.7 (9.0-137.3)		37 (41.1)	53 (58.9)	
Gender	Male	73	32.7 (6.1-106.4)	0.557	41 (56.2)	32 (43.8)	0.371
	Female	127	56.2 (6.3-137.2)		63 (49.6)	64 (50.4)	
F/H of thyroid disorder	Present	21	80.6 (59.0-300.0)	0.006	4 (19.0)	17 (81.0)	0.001
	Absent	179	27.9 (4.7-119.7)		100 (55.9)	79 (44.1)	
Goiter grade	Grade 0	13	38.8 (12.7-126.9)	0.420	7 (53.8)	6 (46.2)	0.682
	Grade 1	64	21.4 (3.7-123.9)		36 (56.3)	28 (43.8)	
	Grade 2	123	56.2 (6.7-132.7)		61 (49.6)	62 (50.4)	
Goiter type	Diffuse	154	18.3 (3.6-116.4)	<0.001	94 (61.0)	60 (39.0)	<0.001
	Nodular	46	99.6 (56.5-209.7)		10 (21.7)	36 (78.3)	
Ophthalmopathy	Present	22	29.6 (5.5-174.5)	0.821	12 (54.5)	10 (45.5)	0.800
	Absent	178	42.7 (6.2-126.0)		92 (51.7)	86 (48.3)	

(Within parenthesis are percentages over row total), p value by Nonparametric tests or Chi-square test as applicable, Tg=Thyroglobulin; F/H=Family history

Table 2: Serum Tg across the subcategories of thyrotoxicosis.

Etiology of thyrotoxicosis	N	Tg level (ng/ml) Median (IQR)	P	Tg status		P value
				Normal N (%)	Elevated N (%)	
All cases	200	42.5 (6.2-126.0)	<0.001	104 (52.0)	96 (48.0)	<0.001
Graves' Disease	137	12.5 (2.9-77.4)		92 (67.2)	45 (32.9)	
Toxic nodular goiter	44	99.6 (56.3-217.8)		10 (22.7)	34 (77.3)	
Subacute thyroiditis	19	132.6 (116.0-232.2)		2 (10.5)	17 (89.5)	

(Within parenthesis are percentages over row total), P value by Nonparametric tests or Chi-square test as applicable

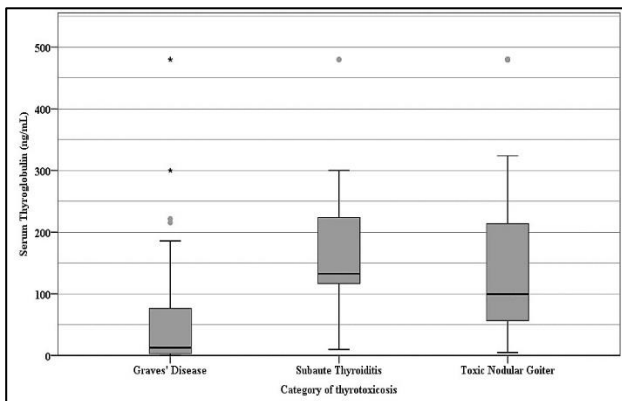


Figure 1: Box-plot presentation of the median Tg among the three groups.

Median Tg levels and the Tg status of the subjects with the three major etiologies of thyrotoxicosis are shown in Table 2. Median Tg was highest in the subjects with subacute thyroiditis, followed by toxic nodular (solitary or multinodular) goiter, whereas those with Graves' disease had the lowest level. The differences among the median Tg levels across the three groups were statistically significant ($p < 0.001$). The frequency of elevated Tg was also highest in the subacute thyroiditis group and lowest in the Graves'

disease; the difference in the rates of elevated Tg across the three groups was also statistically significant ($p < 0.001$). Figure 1 is the box-plot presentation of the median Tg among three groups. The Kernel density plots of serum Tg for the three principal etiologies of thyrotoxicosis are shown in Figure 2

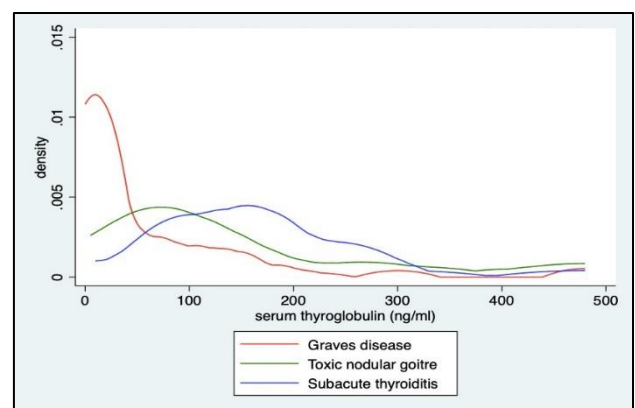


Figure 2: The Kernel density plots of Serum Tg for the three principal etiologies of thyrotoxicosis.

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DISCUSSION

The present study aimed to observe the serum thyroglobulin level in 200 patients with newly detected hyperthyroidism of various etiologies. Tg was higher in the higher age group subjects and those with a family history of thyroid diseases. Median Tg level was highest in the subacute thyroiditis followed by toxic nodular goiter and Graves' disease; the intergroup difference was statistically significant ($p < 0.001$).

Tg is a large, homodimeric glycoprotein (660 KDa) that contains 8% to 10% carbohydrates and iodine. Tg is produced by thyroid follicular cells; T4 and T3 are synthesized on Tg within the lumen of thyroid follicles. The secretion of Tg is TSH-dependent. Most Tg is reabsorbed into thyrocytes and proteolytically degraded during T4 and T3 secretion. However, small amounts of intact Tg are secreted with the thyroid hormones and are detectable in healthy individuals' serum. Tg levels roughly parallel the thyroid glands' size (0.5–1.0 ng/mL Tg per gram of thyroid tissue, depending on the TSH level).¹⁰

A primary clinical value of measuring serum Tg level is in the management, but not in the diagnosis of differentiated thyroid carcinoma.^{3-5,11} Serum Tg concentrations are increased in patients with both benign and differentiated malignant follicular cell-derived tumors of the thyroid and do not serve to distinguish between the two. After total thyroid ablation for papillary or follicular thyroid carcinoma, Tg should not be detectable, and its subsequent appearance typically signifies the presence of persistent disease.¹¹ The serum Tg level is related to the mass of neoplastic tissue and may be undetectable in patients with small lymph node micrometastases.^{5,11} In the hypothyroid newborn, serum Tg is undetectable in patients with thyroid agenesis and is usually elevated in those with ectopic thyroid tissue or goiter and consumptive hypothyroidism due to infantile hemangioma.¹² Serial measurements of serum Tg can help diagnose and monitor subacute "painful" thyroiditis, which may allow a more comprehensible description of the clinical history and pathophysiologic events of painful subacute thyroiditis.⁷ Low rather than elevated concentrations of serum Tg in thyrotoxic patients may indicate the presence of thyrotoxicosis factitia.⁶ Thus, the distinction between the

early phase of subacute thyroiditis and thyrotoxicosis factitia, both of which are characterized by reduced radioactive iodine uptake, may be aided by serum Tg measurement, particularly when the former occurs without neck pain.¹⁴

In Graves' disease, thyroid-stimulating immunoglobulin (TSI) act like TSH to stimulate the thyroid and cause an elevation in serum Tg level.^{13,14} The application of Tg measurement in Graves' disease is limited by the presence of Tg autoantibodies in a substantial number (30%) of such patients, which may result in lower Tg values.⁵ The reason why Tg serum concentration is elevated in nodular thyroid disease is mostly unknown though the failure of exogenous thyroid hormone to suppress serum Tg in these conditions suggests that Tg secretion is, in part, non-TSH mediated.^{15,16} Because of Tg autoantibodies' presence in 60% of patients with Hashimoto's thyroiditis, the measurement of Tg in this condition is of no practical value.¹⁷ Measurement of Tg in serum and thyroid biopsy material helps diagnose congenital dysmorphogenetic goiter.¹⁸ Hidaka et al suggested that relatively higher Tg in postpartum thyroiditis could be used to differentiate it from postpartum Graves' disease where RAIU is contraindicated and if TSI measurement is unavailable.¹⁹

In the present study, the Tg level was higher in the higher (>40 years) age group, and more subjects in this age group had elevated Tg. No age-related variation of the Tg level has been reported in previous studies.²⁰ The median Tg level was higher (not significant) in females than the males, in agreement with a previous study done by Torrigiani et al.¹⁹ Like Torrigiani et al we also observed that patients with a family history of thyroid diseases had a significantly higher serum thyroglobulin level than patients with negative family histories.²⁰ In this study, the Tg level was highest in the subjects with grade 2 goiter followed by grade 1 and grade 0 goiter though the differences among them were insignificant. Serum Tg levels are roughly parallel to the thyroid gland size, and in a study, patients with large goiters had significantly higher values than those with small glands ($p < 0.005$), and patients with medium-sized goiters had intermediate values.^{10,20} This may also explain the higher Tg level and higher frequency of elevated Tg in subjects with nodular goiter than those with diffuse goiter in this study. Furthermore, Rink et al. observed that nodular thyroid tissue led to far higher Tg values than presumed when considering the respective thyroid volume, with a relatively high variance.²¹

In this study, median Tg and the frequency of elevated Tg were highest in subacute thyroiditis and lowest in Graves' disease. There is a scarcity of large-scale studies comparing the Tg levels among various etiologies of thyrotoxicosis. Some researchers observed the most pronounced elevations of serum Tg levels after damage to the thyroid gland, e.g., in active subacute thyroiditis.^{8,22} The active stage of subacute thyroiditis and Graves' disease may be differentiated by Tg levels, especially

when the two conditions' classical features are absent, and thyroid uptake tests are unavailable. Patients with toxic nodular goiter had higher Tg than those with Graves' disease in this study. On the contrary, Feldt-Rasmussen et al. observed no statistically significant difference between the median Tg of the subjects with toxic adenoma and Graves' disease.²³ There is also a considerable overlap of serum Tg levels in Graves' thyrotoxicosis with nontoxic, uninodular, and multinodular goiter in the available literature.^{13,14}

Limitations

No healthy control subjects were evaluated for comparison with the thyrotoxic subjects. Again, it was a tertiary hospital-based single-center study, and the sample may not represent the whole country. Antithyroglobulin antibody was not measured. The iodine-status of the subjects were also not evaluated. Furthermore, serum Tg was measured only once; the sequential Tg measurement would add more information on the trend of Tg level changes in the course of the hyperthyroid conditions.

CONCLUSION

Serum Tg may be useful as an adjunct tool for assessing the differential diagnosis of common etiologies of thyrotoxicosis, especially in the absence of typical clinical presentations of the conditions. A large-scale study with serial measurement of Tg during the disease course may be conducted to justify the value of serum Tg measurement in the differential diagnosis of thyrotoxicosis.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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