Original Article

Rapid Differential Diagnosis of Thyrotoxicosis Using T3/T4 Ratio, FT3/FT4 Ratio and Color Doppler of Thyroid Gland

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Abstract

Context: Establishing the etiology of thyrotoxicosis is of utmost importance to plan the appropriate line of therapy. However, certain scenarios such as absence of pathognomonic clinical features of Graves' disease in some patients, or non-availability of radionuclide scanning and newer generation TRAb assays especially in resource-poor settings, necessitates utilization of other, simple and effective measures to differentiate between the two common causes of thyrotoxicosis, Graves' disease (GD) and Destructive thyroiditis (DT). **Aims:** The aim of this work was to study the role of FT3/FT4 ratio, T3/T4 ratio and color flow Doppler ultrasound in treatment-naïve patients with thyrotoxicosis, in comparison to Tc-99m pertechnetate thyroid scanning in the differentiation of thyrotoxicosis due to GD and DT. **Materials and Methods:** Clinical data was collected from all study subjects. Thyroid function tests including FT3, FT4, T3, T4 and TSH, TSH Receptor Antibody (TRAb), Technetium Tc 99m pertechnetate scan and the mean peak systolic velocity in inferior thyroid artery (mean PSV-ITA) by color Doppler ultrasonography of thyroid gland was done in all patients. **Results:** A total of 83 treatment-naïve patients with thyrotoxicosis (61 with GD and 22 with DT) were studied. Mean PSV-ITA, T3/T4 ratio and FT3/FT4 ratio showed a sensitivity of 85.2%, 73.8%, and 77.04%, and a specificity of 90.9%, 72.7%, and 59.09%, respectively. The three parameters in combination yielded a positive predictive value of 100% in the diagnosis of Graves' disease. **Conclusion:** Results of this study show that inferior thyroid artery blood flow, T3/T4 ratio and FT3/FT4 ratio are useful parameters in the differentiation between GD and DT.

Keywords: Color-flow Doppler, FT3/FT4 ratio, Graves' disease, thyroiditis, T3/T4 ratio

Introduction

Thyrotoxicosis is a state that manifests as a result of excess thyroid hormone action at the tissue level resulting from inappropriately high thyroid hormone concentrations. It may be caused by hyperthyroidism which results from excess production and release by the thyroid gland, or thyrotoxicosis without thyroid gland hyper-function, in which excess level of thyroid hormones is not derived from the thyroid or is derived from the thyroid by excess secretion rather than production,[1] such as destructive thyroiditis. The prevalence of hyperthyroidism in India ranges from 1.2-1.3%.[2] As it a very commonly encountered entity in clinical practice, it is important to delineate the exact etiology of thyrotoxicosis, as management of Graves ' disease (GD) and Destructive Thyroiditis (DT) differs to a great extent.

The latest American Thyroid Association guidelines[3] recommend measurement of TSH Receptor antibody, determination of the radioactive iodine uptake, or measurement of thyroidal blood flow on ultrasonography depending on available clinical expertise and resources. Although the new generation TRAb assays are highly sensitive and specific for discriminating GD from various causes of thyrotoxicosis,[4] these assays are not widely available, and cost remains an important factor when considering their use in routine clinical practice. Radionuclide scanning is frequently used to differentiate Destructive Thyrotoxicosis (DT) from hyperthyroidism. Although iodine-123 sodium iodide [123I-iodide] is an ideal agent for diagnostic thyroid imaging,[5] due to its limited availability and cost,

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technetium-99m sodium pertechnetate [99mTc-pertechnetate] or iodine-131 sodium iodide [131I-iodide] are more commonly used. However, it is contraindicated during pregnancy and lactation,[6] and has limited availability. Additionally, it is not helpful in patients with recent exposure to excessive iodine in the form of iodine-containing drugs, food, and contrast.

Establishing the etiology of thyrotoxicosis, in order to plan the appropriate line of therapy, necessitates utilization of other, simple and effective measures to differentiate between thyrotoxicosis due to GD and that caused by DT, considering the limitations of thyroid radionuclide scanning and TRAb in initial evaluation of thyrotoxicosis, especially in resource-limited settings. There is paucity of data regarding assessing use of free thyroid hormones and PSV in ITA, as parameters for differentiation of GD from other etiologies of thyrotoxicosis in the Asian population. We studied the role of FT3/FT4 ratio, T3/T4 ratio and color flow Doppler ultrasound in treatment-naïve patients with thyrotoxicosis, as simple adjuncts to Tc-99m pertechnetate thyroid scanning and TRAb in the differentiation of thyrotoxicosis due to GD and DT, alone and in combination.

Materials and Methods

Study design and population

This comparative cross-sectional study was conducted at the Department of Endocrinology at a tertiary care teaching hospital in the eastern part of India. A total of 83 patients with thyrotoxicosis of new-onset without history of anti-thyroid drug intake were recruited in the study. All study participants underwent a detailed history enquiry and clinical examination using a preformed proforma. A Technetium (Tc-99m) pertechnetate scan was done in all patients during initial evaluation of thyrotoxicosis. Patients were subdivided into 2 groups for analysis: Patients with DT and patients with GD. A diagnosis of GD was established on the basis of clinical parameters (marked weight loss, adrenergic symptoms, goiter, skin and nail changes, eye signs) and high uptake on Tc-99m thyroid scanning. DT was diagnosed on the basis of low Tc-99m uptake scan, the presence of insignificant symptoms (no or minimal weight loss, occasional palpitations, absent eye signs with or without goiter). In this study, Technetium-99m (99mTc) pertechnetate thyroid scanning was used as the gold standard in differentiating GD from DT. All patients with a normal uptake on Tc-99m pertechnetate scan were excluded from the study as it would be difficult to differentiate mild GD from recovering thyroiditis. Written informed consent was taken from all study participants. The ethical clearance for the study was obtained from our Institutional ethical committee.

Laboratory tests

Serum levels of TSH, free T3, free T4, total T3, total T4 and TSHR antibodies were measured in all patients. Serum was separated in a centrifuge and 2 aliquots were made, one of which was used to immediately measure FT3, FT4, T3, T4 and TSH, whereas the other one was stored for assessing TRAb. Serum FT3 (normal range 3.1–6.8 pmol/L), serum FT4 (normal range 12-22 pmol/L), serum T3 (normal range 84–200 ng/dl), serum T4 (normal range 5.13–14.0 µg/dl) and TSH (normal range 0.27–4.20 microIU/ml) were measured on the day of collection using Electrochemiluminescene Immunoassay (ECLIA) kits (Roche Diagnostics, Mannheim, Germany). ECLIA was performed using automated cobas e 411 analyzer (Roche Diagnostics, Mannheim, Germany). Serum Anti-TSH Receptor antibody (TRAb) (Cutoff-1.75 IU/L with a functional sensitivity of 0.8-40 IU/L) was measured using ECLIA kits (cobas e 411, Roche diagnostics, Germany) in all patients. The manufacturer's instruction mentions Anti- TSHR level >1.75 IU/L to be suggestive of GD.

A radiologist, who was blinded to the full clinical status, performed all thyroid ultrasound examinations. The patients were examined in dorsal decubitus with a cushion under their shoulders with neck in the extended position. Colour Doppler examination of thyroid gland was done by 5-12 MHz linear transducer using PHILIPS HD 7 USG machine. Peak systolic velocity of both the right and left inferior thyroid arteries was assessed; for the purpose of this study, mean inferior thyroid artery flow of right and left lobes was considered.

Statistical analysis

The data were analyzed using IBM SPSS 20 statistical software (IBM Corp., Armonk, NY, USA). The data are expressed as mean ± standard deviation. We used the Chi-square test for categorical data and the independent samples Student's *t* test for parametric quantitative data. Based on previous literature a T3/T4 ratio (ng/µg) cutoff of more than 20,[3] an FT3/FT4 ratio more than 0.3[7] and a mean PSV-ITA of more than 30 cm/s[8] were considered as suggestive of GD. In addition, we did an ROC curve analysis to derive cutoffs. Further, an ROC curve analysis was done to identify cutoffs based on data from our study participants.

Results

A total of 83 consecutive patients participated in this study. Sixty-one patients had destructive thyrotoxicosis, and twenty-two patients had GD. A female preponderance was seen in both the GD group and the DT group [Table 1]. All 83 patients had suppressed TSH levels and increased total T3 and T4 levels. A T3 to T4 ratio (ng/µg) greater than 20 was seen in 45 patients (74%) with GD and in 6 patients (27%) with destructive thyrotoxicosis. This difference in T3/T4 ratio between both groups was statistically significant (P = <0.001) [Table 2]. At a cutoff of 20 (ng/µg), T3/T4 ratio had a sensitivity, specificity and diagnostic accuracy of 73.8%, 72.7%, and 73.49%, respectively. An ROC curve analysis revealed a greater specificity of 95.45% with a sensitivity of 42.62% with a T3/T4 ratio (ng/µg) cutoff of 24. The FT3 and FT4 levels were significantly higher in GD as compared to DT (P = 0.002, P = 0.003, respectively). At a cutoff of 0.30 (pmol/pmol), FT3/FT4 ratio had a sensitivity, specificity and diagnostic accuracy of 77.04%, 59.09% and 72.2%, respectively, in the differentiating

GD from DT. Mean PSV-ITA was significantly higher in patients with GD than in patients with DT (51.64 ± 24.53 cm/s versus 21.77 ± 6.15 cm/sec, $P < 0.001$) [Table 3]. A ROC curve analysis of the mean PSV-ITA values yielded an area under the curve (AUC) of 0.942, with a cutoff value of 29.5 cm/sec emerging as an appropriate value to differentiate between GD and thyroiditis. Using a combination of mean PSV in ITA, FT3/FT4 ratio and T3/T4 ratio a sensitivity of 55.74%, specificity of 100% with a positive predictive value of 100% was obtained in the diagnosis of GD compared to Tc-99m thyroid scintigraphy.

Discussion

Thyrotoxicosis is a commonly encountered entity, and many etiologies may contribute to it. It is crucial to carry out an appropriate evaluation to identify the accurate etiology of thyrotoxicosis as suitable management varies based on the cause. Although clinical measures aids considerably in diagnosis, it may be challenging to ascertain the etiology of thyrotoxicosis in the absence of diffuse goiter or pathognomonic features of GD such as ophthalmopathy. When it is not possible to obtain a thyroid scan or TRAb due to limited availability, affordability issues or presence of contraindications for a scan, the challenge to differentiate between the two conditions increases even further. Data regarding FT3/FT4 ratio, T3/T4 ratio and use of color flow Doppler ultrasound in differentiation of the two conditions is scarce in the Asian population. To the best of our knowledge, this is the first study looking into a combination of these factors for delineation of etiology of thyrotoxicosis.

Measurement of biochemical parameters like thyroid hormone levels has been suggested to help identify the etiology of the thyrotoxicosis.[9] T3/T4 ratio has been considered as an ancillary tool in delineating the etiology of thyrotoxicosis, with a T3/T4 ratio (ng/μg) of > 20 suggestive of GD[3] and a ratio less than 20 as a marker of destructive thyrotoxicosis.[10] In our study, 73% of patients with DT had a T3 to T4 ratio less than 20, but this was also true in 26% of patients with GD. Our results are in concordance with Yanagisawa T. *et al*.[11] who demonstrated that 75.5% patients with GD had a T3/T4 ratio (ng/μg) >20 and a similar diagnostic performance in the diagnosis of GD, as that seen in our study. This indicates a marked overlap between the conditions when using the T3 to T4 ratio as a criterion, as also observed by others.[9] The T3/T4 ratio is also limited by the fact that, total T3 and total T4 levels are affected by thyroxine binding globulin (TBG) concentration. Although ROC curve analysis revealed a greater specificity of 95.45% at a T3/T4 ratio (ng/μg) cutoff of 24, this needs to be validated in larger studies.

Although the ratio of total T3 to total T4 is commonly used for differentiating the etiology of thyrotoxicosis between GD and thyroiditis, free thyroid hormone (FT3 and FT4) measurements are frequently ordered in current clinical practice.[12] Various studies have explored the use of FT3/FT4 ratio in determining the etiology of thyrotoxicosis.[7,13,14] However, there is considerable overlap of the values of this parameter.[9,14] Based on a recent study,[7] using a cutoff of >0.30 suggestive of GD, we obtained a sensitivity of 77.04%, specificity of 59.09%, positive predictive value of 83.92% and a diagnostic accuracy of 72.2% in the differential diagnosis of thyrotoxicosis. Further, an ROC curve analysis of FT3/FT4 ratio (pmol/pmol) revealed an optimal cutoff range of 0.28-0.32 for FT3/FT4 ratio, with a sensitivity of up to 85.2% and specificity of up to 63.6% in the diagnosis of GD. In a study by Baral S, *et al*.[7] an FT3/FT4 ratio cutoff of 0.30 was found to be useful in differentiating GD

Table 1: Characteristics of study population

Variable	Graves' disease	Destructive Thyroiditis	*P*
Age (in years)	38.43±12.61	35.77±12.52	0.001
BMI (in Kg/m^2)	18.83±2.43	20.59±1.39	0.38
Gender distribution			
Female	42 (68.9)	16 (72.7)	0.79
Male	19 (31.1)	6 (27.3)	

Values mentioned in mean±SD, *n* (%)

Table 2: Various biochemical and imaging parameters in the study groups

Variable	Group		*P*
	GD	DT	
T3 (ng/dl)	475±114	411±148	0.025
T4 (μg/dl)	20.93±3.21	20.81±3.92	0.63
FT3 (pmol/L)	28.48±13.95	18.28±12.03	0.002
FT4 (pmol/L)	75.04±27.92	55.21±25.69	0.003
TSH (mIU/ml)	0.03±0.1	0.05±0.07	0.004
FT3:FT4 ratio (pmol/pmol)	0.41±0.34	0.31±0.06	0.002
T3/T4 ratio (ng/μg)	22.52±3.99	17.78±3.54	<0.001
Uptake total (%)	19.73±10.43	0.09±0.18	<0.001
TRAb (IU/L)	23.38±12.06	2.61±1.92	<0.001
Mean PSV-ITA (cm/sec)	51.64±24.53	21.77±6.15	<0.001

Values mentioned in mean±SD

Table 3: Diagnostic ability of TRAb, mean PSV-ITA, T3/T4 ratio and FT3/FT4 ratio in the differential diagnosis of thyrotoxicosis

Parameter	Cutoff	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
TRAb	1.75 IU/L	100	36.4	100	81.33
Mean PSV-ITA	30 cm/sec	85.2	90.9	68.97	96.3
T3/T4 ratio	20 ng/μg	73.8	72.7	50	88.24
FT3/FT4 ratio	0.3 pmol/pmol	77.04	59.09	48.14	83.92

from DT, with a sensitivity of 87% and specificity of 62.5%, which was similar to results obtained in our study. In a study by Chen X, *et al*.[14] FT3/FT4 ratio was able to differentiate GD from DT with a sensitivity of 87.3% and a specificity of 91.4% with an AUC of 0.940 (95% CI: 0.912–0.969). They proposed that an enhanced DIO1 might at least partly contribute to the higher FT3/FT4 ratio in patients with GD. The cutoff of derived in our study was lower than that obtained by the aforementioned study. This may be attributed to variability in assays of FT3. In our study, we also found that the FT3/FT4 ratio correlated with the titers of TRAb.

In our study, the mean PSV-ITA value was significantly higher in patients with GD compared with those with thyroiditis and showed a diagnostic accuracy of 86.75% in the differentiation between the two conditions compared to thyroid scanning by Tc-99m pertechnetate. Further by ROC analysis, we obtained a similar mean PSV in ITA cutoff value of 29.5 cm/sec, at a sensitivity of 91.8% and specificity of 90.9%. A study by Malik *et al*.[8] showed that measurement of PSV-ITA by CFDU is a good diagnostic approach to discriminate between GD and thyroiditis with a sensitivity of 91% and specificity of 89% to differentiate between the two conditions at a cutoff level of 30 cm/s, which was similar to that obtained in our study. Our results are also in agreement with those of Kurita and cols.[15] who showed a sensitivity of 84% and specificity of 90% for CFDU in the differential diagnosis of thyrotoxicosis. A study by Hari Kumar *et al*.[16] showed a sensitivity of 96% and a specificity of 95% in the differential diagnosis of thyrotoxicosis. Another study by Donkol *et al*.[17] showed that Color-flow Doppler ultrasonography parameters showed a sensitivity of 88.9% and a specificity of 87.5% in the differential diagnosis of thyrotoxicosis. Both these studies used a cutoff of > 40 cm/s for the diagnosis of GD. Considering the variations in cutoff for mean PSV in ITA in different studies, larger studies are required for the determination of the same.

When mean PSV in ITA and T3/T4 ratio were used in combination, a sensitivity of 73.33%, a specificity of 72.72%, and a positive predictive value of 88.23% were obtained. However when mean PSV in ITA, FT3/FT4 ratio and T3/T4 ratio were used in combination, a sensitivity of 55.74% and specificity of 100% was obtained. Patients who had all three positive parameters had a positive predictive value of 100% to differentiate GD from DT, implying that in the absence of thyroid radionuclide scanning or TRAb, these simple parameters may be useful to differentiate GD from DT.

The strengths of the study include the use of multiple modalities for the diagnosis of GD, which in addition to nuclear scanning included measurement of TRAb levels as well. Limitations of the study include a small sample size and its cross-sectional nature. As we did not measure urinary iodine, we could not determine the iodine nutritional status among included patients, which might have affected the rate of uptake by the thyroid on Tc-99m pertechnetate scanning. Thyroid ultrasonography examination is operator dependent. To address this, we assigned a single radiologist to perform ultrasonography on all patients. Single operator findings would have probably reduced the inter-observer variations in the determination of PSV values in ITA.

Conclusion

In conclusion, the results of this study show that inferior thyroid artery blood flow, T3/T4 ratio and FT3/FT4 ratio alone or in combination are useful parameters in the differentiation between GD and DT. Measurement of these parameters should be considered for a rapid differential diagnosis of thyrotoxicosis, in order to expedite decision making towards the appropriate line of management, especially when it is not possible to do a thyroid radionuclide scanning/TRAb due to non-availability, affordability issues or presence of coexisting conditions that constitute as contraindications for thyroid radionuclide scanning. However larger, prospective studies are required to confirm these findings.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Sharma A, Stan MN. Thyrotoxicosis: Diagnosis and management. Mayo Clin Proc 2019;94:1048-64.
2. Unnikrishnan AG, Menon UV. Thyroid disorders in India: An epidemiological perspective. Indian J Endocrinol Metab 2011;15(Suppl 2):S78-81.
3. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, *et al*. 2016 American thyroid association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid 2016;26:1343-421.
4. Kamath C, Adlan MA, Premawardhana LD. The role of thyrotrophin receptor antibody assays in Graves' disease. J Thyroid Res 2012;2012:525936.
5. Dhingra VK. Nuclear scanning in evaluation and treatment of thyroid disorders: A beginners guide. Clin Oncol 2017;2:1260.
6. Giovanella L, Avram AM, Iakovou I, Kwak J, Lawson SA, Lulaj E, *et al.* EANM practice guideline/SNMMI procedure standard for RAIU and thyroid scintigraphy. Eur J Nucl Med Mol Imaging 2019;46:2514-25.
7. Baral S, Shrestha PK, Pant V. Serum free T_3 to free T_4 ratio as a useful indicator for differentiating destruction induced thyrotoxicosis from Graves' disease. J Clin Diagn Res 2017;11:OC12-4.
8. Malik SA, Choh NA, Misgar RA, Khan SH, Shah ZA, Rather TA, *et al*. Comparison between peak systolic velocity of the inferior thyroid artery and technetium-99m pertechnetate thyroid uptake in differentiating Graves' disease from thyroiditis. Arch Endocrinol Metab 2019;63:495-500.
9. Izumi Y, Hidaka Y, Tada H, Takano T, Kashiwai T, Tatsumi K-i,

et al. Simple and practical parameters for differentiation between destruction-induced thyrotoxicosis and Graves' thyrotoxicosis. Clin Endocrinol (Oxf) 2002;57:51-8.
10. Amino N, Yabu Y, Miki T, Morimoto S, Kumahara Y, Mori H, *et al.* Serum ratio of triiodothyronine to thyroxine and thyroxine-binding globulin and calcitonin concentrations in Graves' disease and destruction induced thyrotoxicosis. J Clin Endocrinol Metab 1981;53:113-6.
11. Yanagisawa T, Sato K, Kato Y, Shimizu S, Takano K. Rapid differential diagnosis of Graves disease and painless thyroiditis using total T3/T4 ratio, TSH, and total alkaline phosphatase activity. Endocr J 2005;52:29-36.
12. Thienpont LM, Uytfanghe KV, Poppe K, Velkeniers B. Determination of free thyroid hormones. Best Pract Res Clin Endocrinol Metab 2013;27:689-700.
13. Sriphrapradang C, Bhasipol A. Differentiating Graves disease from subacute thyroiditis using ratio of serum free triiodothyronine to free thyroxine. Ann Med Surg (Lond) 2016;10:69-72.
14. Chen X, Zhou Y, Zhou M, Yin Q, Wang S. Diagnostic values of free Triiodothyronine and free Thyroxine and the ratio of free Triiodothyronine to free Thyroxine in thyrotoxicosis. Int J Endocrinol 2018;2018:4836736.
15. Kurita S, Sakurai M, Kita Y, Ota T, Ando H, Kaneko S, *et al*. Measurement of thyroid blood flow area is useful for diagnosing the cause of thyrotoxicosis. Thyroid 2005;15:1249-52.
16. Hari Kumar KV, Pasupuleti V, Jayaraman M, Abhyuday V, Rayudu BR, Modi KD. Role of thyroid Doppler in differential diagnosis of thyrotoxicosis. Endocr Pract 2009;15:6-9.
17. Donkol RH, Nada AM, Boughattas S. Role of color Doppler in differentiation of Graves' disease and thyroiditis in thyrotroxicosis. World J Radiol 2013;5:178-83.