CAN COLOUR FLOW DOPPLER REPLACE RADIO-ISOTOPE SCANNING IN THE DIFFERENTIAL DIAGNOSIS OF THYROTOXICOSIS?

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ABSTRACT

Objective: To evaluate the role of thyroid blood flow assessment by color-flow Doppler ultrasonography in the differential diagnosis of thyrotoxicosis and compare it to Technetium pertechnetate thyroid scanning.

Patients and Methods: Twenty-six patients with thyrotoxicosis were included in the study. History, clinical examination and thyroid function tests including autoantibodies were done for all patients. Thyroid glands of all patients were evaluated by color-flow Doppler ultrasonography for size, vascularity, echotexture and blood flow in the inferior thyroid arteries. Technetium99 pertechnetate scanning of the thyroid was done for all patients.

Results: All patients had suppressed thyrotropin. According to Technecium pertechnetate scanning the 26 patients were divided into 18 cases with Graves' disease and 8 cases with thyroiditis. Thyroid blood flow, as measured by peak systolic velocity of the inferior thyroid arteries, was significantly higher in patients with Graves' disease than in patients with thyroiditis (P value=0.004 in the right inferior thyroid artery & P value=0.001 in left inferior thyroid artery). Diagnosis of Graves' disease and thyroiditis was supported by clinical picture and follow up of patients. Color-flow doppler ultrasonography parameters demonstrated a sensitivity of 88.9% and a specificity of 87.5% in the differential diagnosis of thyrotoxicosis.

Conclusion: Color Doppler flow of the inferior thyroid artery can be used in the differential diagnosis of thyrotoxicosis especially when scanning of the thyroid by radioactive material cannot be done for any reason.

INTRODUCTION

Thyrotoxicosis refers to the hypercatabolic state resulting from elevated serum levels of thyroid hormone mainly free tetraiodothyronine(T4) and/or triiodothyronine(T3). Thyrotoxicosis is not synonymous to hyperthyroidism.It may be caused either by hyperthyroidism or by inflammation of the thyroid with release of stored thyroid hormone but not accelerated synthesis. It may also be caused by ingestion of exogenous thyroid hormone (1).

Hyperthyroidism with diffuse thyroid disease is caused by Graves' disease while thyrotoxicosis due to destructive thyroiditis includes various subsets like lymphocytic thyroiditis, subacute thyroiditis, and postpartum thyroiditis (2-5).

Differentiation between Graves' disease and thyroiditis is very important as management of each case is completely different. Absence of specific signs of Graves disease like ophthalmopathy, skin and nail changes may make it difficult to distinguish it from thyroiditis especially when the disease is mild or subclinical. Nuclear imaging by technetium99 pertechnetate (Tcm99) or iodine 123 radioisotopes is used for this purpose. Measuring thyrotropin (TSH)| receptor antibody levels can be also used. However these methods are not usually available. Nuclear imaging is expensive and contraindicated during pregnancy and lactation (6).

Thyroid hypoechogenicity at ultrasound is a characteristic of autoimmune thyroid diseases, with an overlap of this echographic pattern in patients affected by Graves' disease or Hashimoto's thyroiditis. However, a diffusely increased thyroid blood flow is pathognomonic of untreated Graves' disease and an abnormal color flow Doppler (CFD) pattern identifies the

majority of Graves' patients with a normal thyroid ultrasound pattern. Thus, color flow doppler ultrasonography may be useful in distinguishing patients with Graves' disease and Hashimoto thyroiditis having a similar thyroid echographic pattern at ultrasound (7).

Color flow Doppler ultrasonography is a useful, inexpensive, and non-invasive and widely available method for measuring tissue vascularization and blood flow. The evaluation can be both qualitative (visual assessment of thyroid vascularity) and quantitative (peak systolic velocity, end diastolic velocity and mean velocity in the inferior thyroid arteries). Color flow Doppler ultrasonography of the thyroid gland can provide valuable information about underlying thyroid functional status and is useful in the differential diagnosis of thyrotoxicosis (7-10).

Evaluation of efficiency of color flow Doppler in the differential diagnosis of thyrotoxicosis and comparing its sensitivity and specificity to Tcm99 thyroid uptake is essential to know if both investigations can be used as alternatives in cases of thyrotoxicosis.

PATIENTS AND METHODS

The study was approved by the Research and Ethics committee of Asir Central hospital and written informed consents were acquired from all patients.

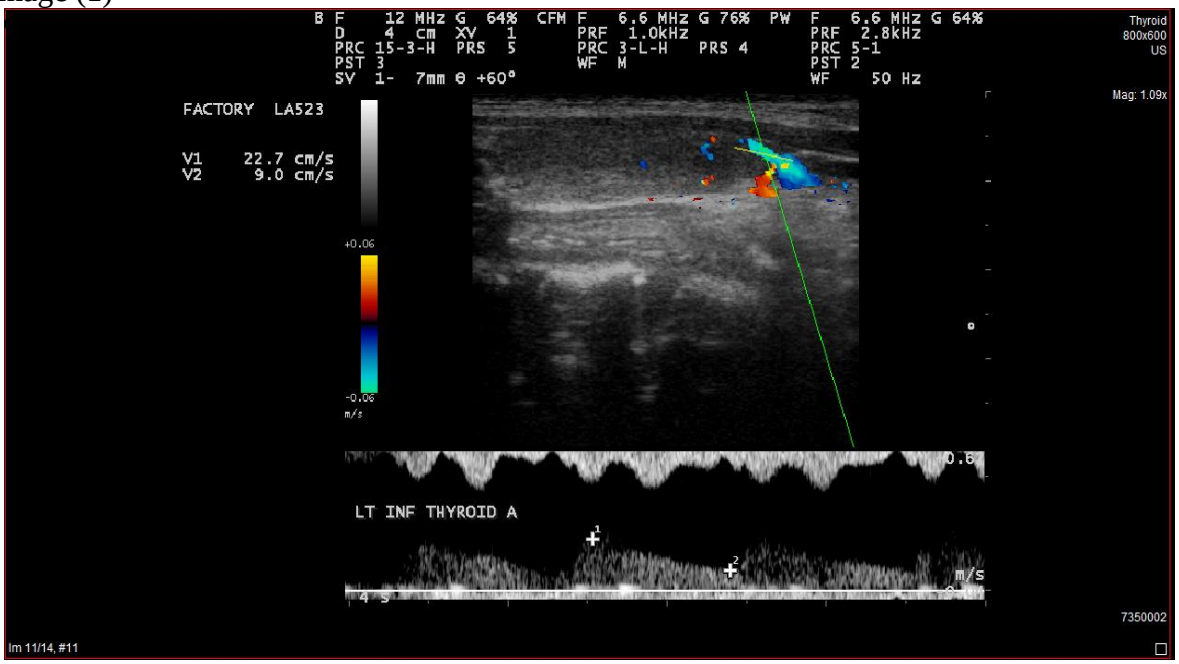
The study population consisted of 26 patients presenting to endocrine clinic with thyrotoxicosis during the period from January to July, 2011. Exclusion criteria included: toxic nodule, history of thyroid surgery, radioiodine therapy or radiation exposure to neck. Patients whose goiter was multinodular or diffuse were included in the study. History including sex and age and clinical examination was done. Measurement of TSH, free T3, and free T4 was performed in all participants. Antithyroid peroxidase and antithyroglobulin antibodies were also measured in all patients.

Graves' disease was diagnosed on the basis of clinical parameters (marked weight loss, adrenergic symptoms, goiter, skin, nail changes and eye signs) and high uptake on Tcm99 thyroid scanning. Thyroiditis was diagnosed on the basis of low Tcm99 uptake scan, the presence of insignificant symptoms (no or minimal weight loss, occasional palpitations, absent eye signs with or without goiter) or later development of hypothyroidism.

All thyroid ultrasound examinations were performed by the same radiologist with twenty years of ultrasound experience who was blinded to the full clinical status and isotopic thyroid scan of the subject. A color Doppler ultrasound scanner (iU22, Philips Ultrasound, Bothell, WA, USA) equipped with a 9 to 3 MHz broadband linear array transducer was used. The grey scale ultrasound examinations of the thyroid gland were performed regarding the size, shape and echotexture of the gland as well as presence or absence of nodules. The color Doppler pattern of the glands were studied and the Doppler spectral analysis of the right and left inferior thyroid arteries were performed with transverse scanning, in which the vessels crossed the common carotid arteries posteriorly, or with longitudinal scanning of the ascending parts of the arteries, in which the vessels lay parallel to the common carotid arteries. The angle correction cursor was parallel to the direction of flow, and the Doppler angle was kept at or below 60°. The peak systolic velocity (PSV), end diastolic velocity (EDV) and mean velocity (MV) were obtained.

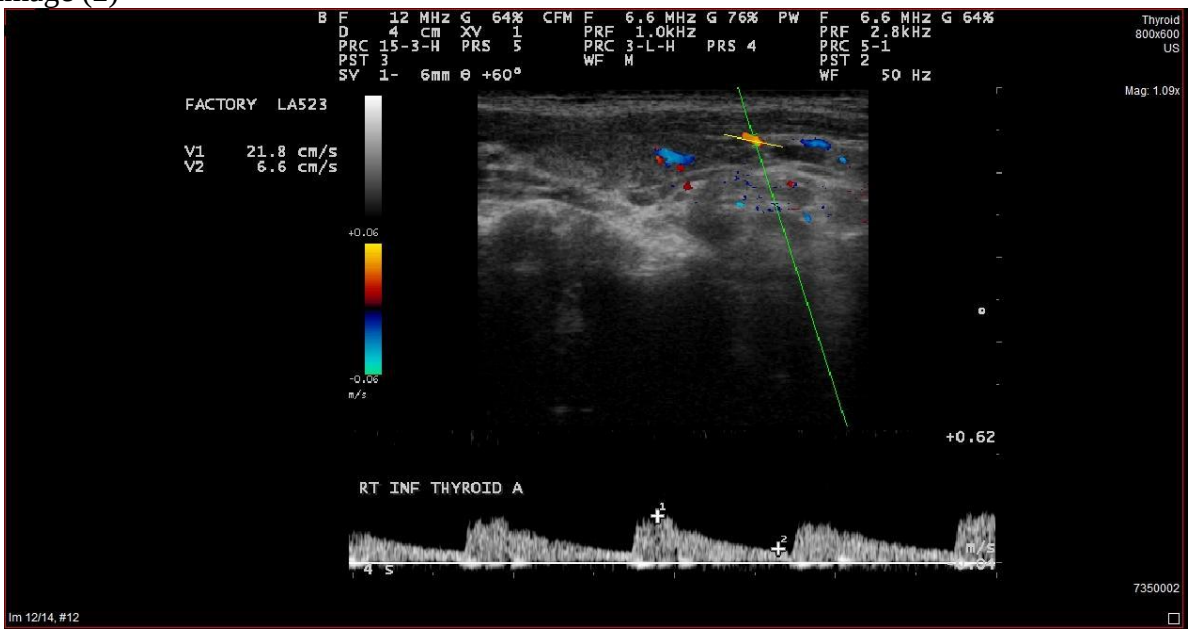
Peak systolic velocity of inferior thyroid artery of 40cm/sec is considered significantly high and suggestive for Graves' disease (11,12). Technetium pertechnetate scan was done in all patients as the gold standard test for differentiation between both conditions at time of diagnosis (Images 1,2 and 3 are for a patient with destructive thyrotoxicosis, while images 4,5 and 6 are for another patient with Graves'disease).

Image (1)



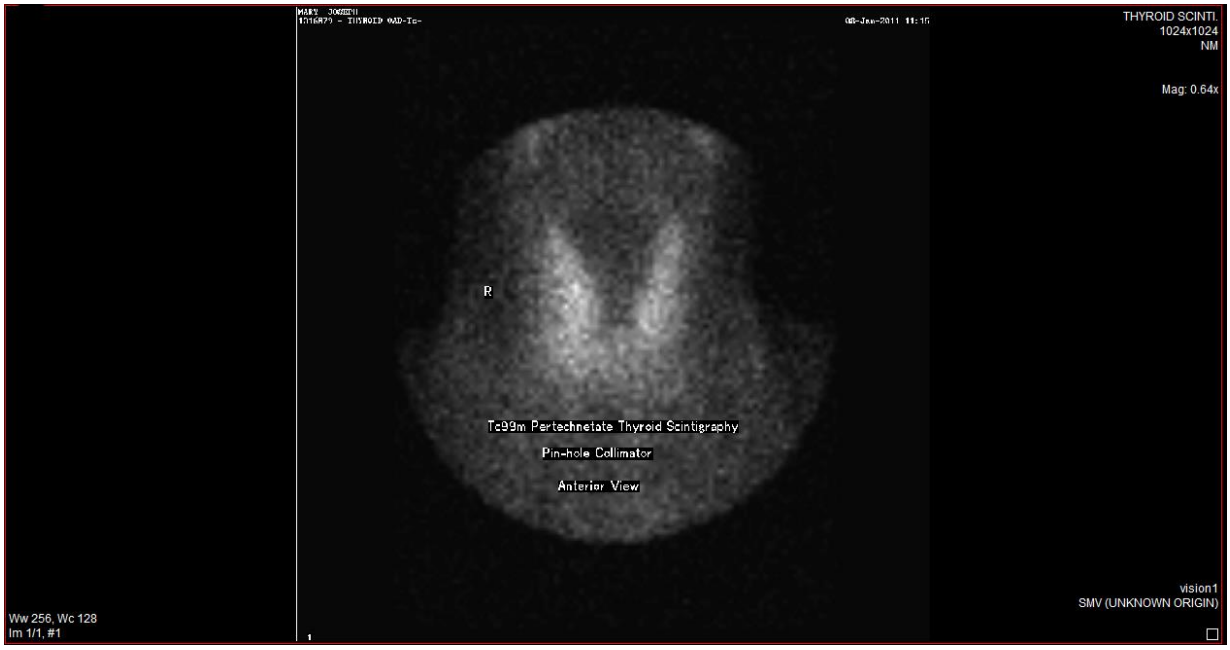
Low CFD of left inferior thyroid artery in a patient with destructive thyrotoxicosis.PSV=22.7cm/sec, EDV=9cm/sec.

Image (2)



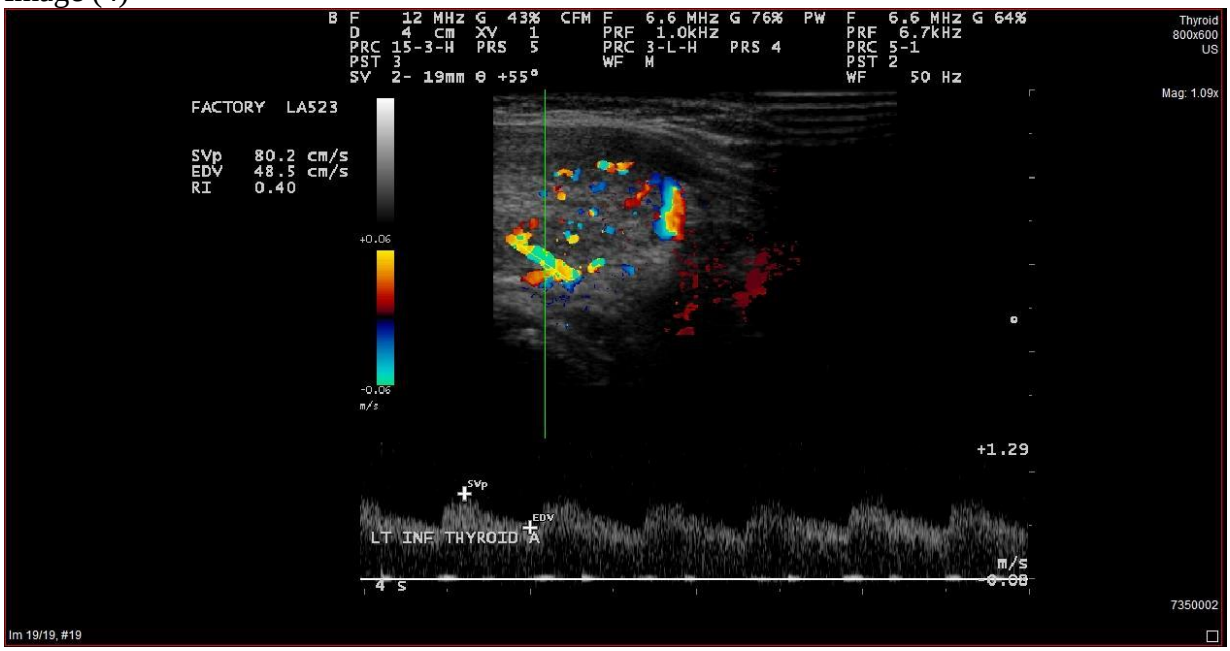
Low CFD of right inferior thyroid artery in the same patient with destructive thyrotoxicosis.PSV=21.8cm/sec, EDV=6.6cm/sec.

Image (3)



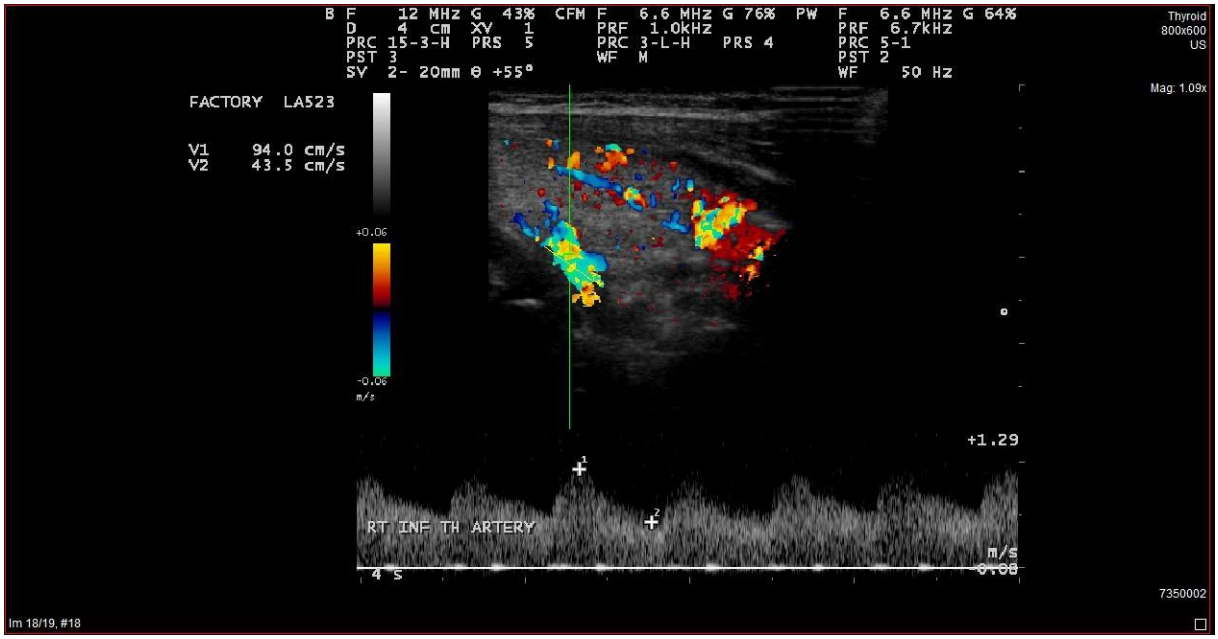
Tcm99 uptake in the same patient with destructive thyrotoxicosis showing uniform low uptake throughout the gland. Uptake was 0.4%.

Image (4)



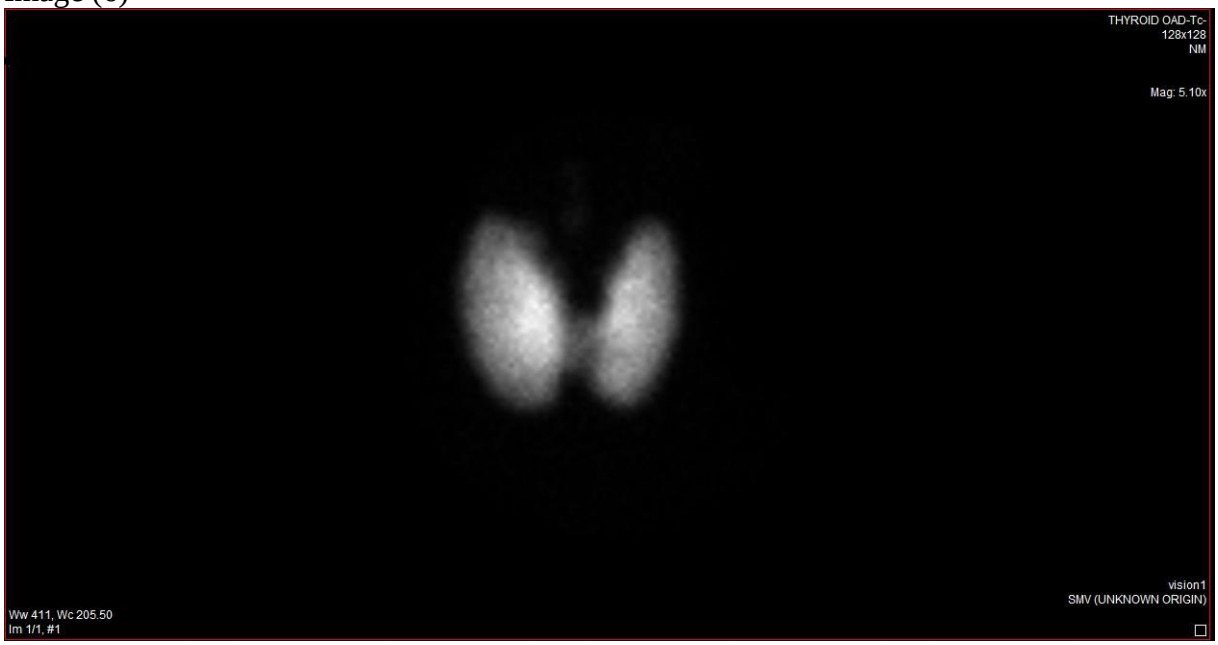
High CFD of left inferior thyroid artery in a patient with Graves'disease. PSV=80.2cm/sec, EDV=48.5cm/sec.

Image (5)



High CFD of right inferior thyroid artery in the same patient with Graves'disease. PSV=94.0cm/sec, EDV=43.5cm/sec.

Image (6)



Tcm99 uptake in the same patient with Graves'disease showing uniform high uptake throughout the gland. Uptake was 29 %.

STATISTICAL ANALYSIS

Frequency, arithmetic mean and standard deviation were used to resent the data. Student "t" test was used as a test of significance at 5% level. To test Screening Test Evaluation with Positive/Negative outcomes, Sensitivity, Specificity, Positive and negative predictive values, and

Likelihood ratios for positive and negative tests were calculated with the concomitant 95% confidence intervals.

RESULTS

A total of 26 patients participated in this study. All have suppressed TSH level (0.08-0.005 microinternational unit/milliliter) with normal or high free T4 and T3 levels. Thyroid scanning by Tcm99 was done for all patients as the gold standard test for differentiation between Graves's and thyroiditis. Supported by the clinical picture of patients, eighteen patients had Graves' disease and eight patients had destructive thyrotoxicosis as per Tcm99 uptake. Reference range for Tcm99 uptake was 0.5% to 3%. Uptake less than 0.5% was considered low while uptake more than 3% was considered high. No significant difference in age between both groups (*p-value = 0.565*).

Thyroid blood flow, as assessed by PSV of the inferior thyroid arteries, was significantly higher in patients with Graves' disease than in patients with destructive thyroiditis (*P- value= 0.004* in the right inferior thyroid artery & *p-value=0.001,* in the left inferior thyroid artery).

End diastolic velocity was significantly higher in Graves' patients than in patients with thyroiditis (*p-value= 0.007,* in the right inferior thyroid artery & *p-value= 0.001* in the left inferior thyroid artery). Consequently, mean velocity in inferior thyroid artery was significantly higher in patients with Graves' than in patients with thyroiditis.

All but two of the patients diagnosed as Graves' disease by cm99 scan had inferior thyroid artery (ITA) flow velocity greater than 40 centimeter/second. Diagnosis of Graves' disease was established in these two patients by increased uptake on pertechnetate scan and symptoms and signs highly in favour of Graves'. All but one of the patients in the destructive thyroiditis group had inferior thyroid artery flow less than 40 centimeter/second. This patient was diagnosed as thyroiditis by low Tcm99 uptake. Diagnosis was always supported by clinical picture and follow up of patients.

Comparing volume of the thyroid gland between both groups revealed significantly larger volume in Graves' patients than in patients with thyroiditis (*p -value= 0.028*).Table (1)

Color Flow Doppler showed a sensitivity of 88.9% and a specificity of 87.5%, positive predictive value of 94.1%, negative predictive value of 77.8% and a diagnostic accuracy of 88.5% in the differential diagnosis of thyrotoxicosis as compared to thyroid scanning by Tcm99 petechnetate. Table (2)

Table (1) Comparing parameters between hyperthyroidism and thyroiditis

Parameter	Graves	Thyroiditis	P-value
Age(mean-SD)in years	**31.1 ± 8.4**	**33.1 ± 7.5**	**0.565**
Thyroid volume in cubic cm	**24.2 ± 10.1**	**14.8 ± 7.54**	**0.028**
RPSV cm/sec	**50.4 ± 23.4**	**21.7 ± 14.8**	**0.004**
REDV cm/sec	**31.3 ± 16.6**	**12.8 ± 9.4**	**0.007**
RMV cm/sec	**68.9 ± 31.6**	**30.6 ± 20.3**	**0.004**
LPSV cm/sec	**49 ± 25.7**	**17.8 ± 6**	**0.001**
LEDV cm/sec	**29.6 ± 17.5**	**10 ± 4.5**	**0.001**
LMV cm/sec	**68.4 ± 35.2**	**25.5 ± 8.3**	**0.001**

RPSV: right peak systolic velocity, REDV: right end diastolic velocity, RMV: right man velocity, LPSV: left peak systolic velocity, LEDV: left end diastolic velocity, LMV: left mean velocity, cm: centimeter, sec: second

Table (2) Sensitivity and Specificity of CFD

Parameter	Estimate	Lower-Upper95% CIs
Sensitivity	**88.9%**	**67.2 - 96.9**
Specificity	**87.5%**	**52.9 - 97.8**
Positive Predictive value	**94.1%**	**73.0 - 99**
Negative Predictive value	**77.8%**	**45.3 - 93.7**
Diagnostic accuracy	**88.5%**	**71 - 96**
Likelihood ratio of a positive Test	**7.1**	**0.99 - 51.3**
Likelihood ratio of a negative Test	**0.1**	**0.05 - 0.4**
Diagnostic Odds	**56**	**4.3 - 724.1**
Cohen's kappa (Unweighted)	**0.7**	**0.4 - 1.1**

CFD: colour flow doppler

DISCUSSION

Clinical manifestations of thyrotoxicosis in cases of thyroiditis and early or mild Graves disease may be difficult to differentiate. Although persistence of symptoms and signs in Graves' disease can distinguish it from thyroiditis, it is very important to diagnose the diasease early for the proper management. Nuclear uptake scan of the thyroid is one of the definitive diagnostic tools especially when there is confusion between both conditions. However, limited availability, high cost, and contraindications to radioisotope scan during pregnancy and lactation restrict their application.

Although radioactive iodine is often useful in the diagnosis and treatment of thyrotoxicosis, such tests cannot be performed in many patients because of recent use of iodinated contrast for other diagnostic studies, such as computed tomography (CT) scanning. In their study, Phillips and Hennessey found that 45% of patients with newly diagnosed thyrotoxicosis had received iodinated contrast within 2 weeks before endocrinology evaluation; 43% had received iodine for CT and the other 2% for angiography (13).

In our study, Tcm99 pertechnetate was used as the definitive radiological investigation to differentiate the two types of thyrotoxicosis. Thyroid blood flow was evaluated as a parameter to differentiate types of thyrotoxicosis and to compare its sensitivity and specificity to Tcm99 uptake by the thyroid.

Peak Systolic Velocity, EDV and mean inferior thyroid artery flow in patients with Graves' disease was significantly higher in patients with Graves' than in patients with thyroiditis. Bogazzi et al, 1999 reported similar finding when he noticed increased intraparenchymal peak systolic velocity in Graves' disease but not in destructive thyrotoxicosis (14).

Color flow Doppler ultrasonography in our study showed a sensitivity of 88.9% with specificity of 87.5%. These results are comparable to the results of a study carried out by Kurita et al on 75 patients with thyrotoxicosis, which demonstrated that CFD ultrasonography had a sensitivity of 84% and specificity of 90% in the differential diagnosis of thyrotoxicosis (15).

On the other hand, Kumar et al, 2009; in a study of 65 patients with thyrotoxicosis, found significantly higher blood flow in inferior thyroid arteries in Geaves' than in destructive throtoxicosis. He also demonstrated that CFD ultrasonography had a sensitivity of 96% and a specificity of 95% in the differential diagnosis of thyrotoxicosis(16).

Other forms of thyroid blood flow assessment like thyroid blood flow area, vascularization index, and high-resolution power Doppler have been used by investigators to provide better differentiation (4,17).

Refering to various studies, CFD ultrasonography of the thyroid gland is considered as one of the initial investigations that can give great help in the differential diagnosis of thyrotoxicosis especially that it is a simple technique with no radiation exposure and is also cost effective (18,19).

CONCLUSION

Inferior thyroid artery blood flow is a useful parameter in the differential diagnosis of thyrotoxicosis. It has a sensitivity of 88.9% with a specificity of 87.5% in the differentiation between Graves' disease and other forms of autoimmune thyoiditis. It is an acceptable alternative to radio-isotope scan, especially, when there is contraindication to nuclear imaging of the thyroid. We recommend measurement of thyroid blood flow in ITA as an essential part of initial investigations of thyrotoxicosis.

Declaration of interest

The authors have no conflict of interest.

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