Original Article

# Role of doppler ultrasonography in thyrotoxicosis — differentiation between Graves' disease and sub-acute thyroiditis

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**Graves' disease (GD) and sub-acute thyroiditis (SAT) are among the commonest causes of thyrotoxicosis. It is prudent to differentiate them because management in terms of subsequent diagnostic evaluation and management is totally disease specific. But it is often difficult to make this distinction without measurement of radioactive iodine uptake (RAIU) which considered as a reference standard. But this facility is not available in most of the smaller cities and towns of India. Color flow doppler ultrasonography which is much more readily available and cheaper allows direct measurement of thyroid function through real-time detection of tissue vascularization and blood flow. In this study 57 patients of thyrotoxicocis after exclusion of toxic nodules were evaluated. Detailed history and physical examination was done with relationship to those pertinent to thyrotoxicosis such as goiter, tachycardia, tremor, eye changes including ophthalmopathy. Thyroid profile was performed. USG including colour Doppler, fine needle aspiration cytology and haemogram were also performed. Tremor, restlessness, palpitation, increased appetite and prominence of eyes were commoner in GD. History of antecedent was present in half of SAT. ESR was much higher in SAT. There was no difference in thyroid profile between them. Increased intrathyroidal blood flow and increased peak systolic velocity (PSV) of inferior thyroid artery (ITA) above 50cm/second has been usually found in hyperthyroidism whereas they are normal or slightly increased in sub-acute thyroisitis.**

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***Key words*** **: Graves' disease, sub-acute thyroiditis, radioactive iodine uptake, inferior thyroid artery, peak systolic velocity**

Graves' disease (GD) and destructive thyroiditis are the causes of thyrotoxicosis[1]. It is prudent to differentiate them because management in terms of subsequent diagnostic evaluation and management is totally disease specific[2]. But it is often difficult to make this distinction without measurement of radioactive iodine uptake (RAIU) which is the traditional approach and considered as a reference standard[3,4]. Color flow doppler ultrasonography (CFDUS) is a noninvasive technique that allows direct measurement of thyroid function through real-time detection of tissue vascularization and blood flow[5,6]. Increased intrathyroidal blood flow especially the "thyroid-inferno" pattern and increased peak systolic velocity (PSV) of inferior thyroid artery (ITA) has been usually found in hyperthyroidism whereas they are normal or decreased in the latter[7,8].

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## Materials and Methods

Consecutive adult patients attending endocrine clinic within October 2015 to September 2017 with clinical and biochemical features of thyrotoxicosis were included in the study population after obtaining informed consents. Patients with toxic nodule and multi nodular goitre were excluded. Detailed history of the participants were taken emphasizing mostly upon palpitations, tremors, weight loss, increased appetite, eye changes, antecedent fever, sore-throat and other hyperthyroid symptoms. The patients having history of thyroid surgery, radioiodine therapy, previous radiation exposure to neck were excluded from the study. Clinically, the participants were assessed for tachycardia, tremors, goitre, thyroid bruit and the typical symptoms of GD like ophthalmopathy, skin and nail changes etc. Then they were divided into 2 groups: Graves' disease and subacute thyroiditis (SAT), a subtype of destructive thyroiditis, after considering their thyroid function

tests, complete haemogram and fine needle aspiration cytology (FNAC) findings.

Target of our cross- sectional study was to evaluate the role of CFDUS in differentiation of these two diseases hence both the groups underwent thyroid grayscale USG and size and echogenicity of the gland were noted. Normal parameters for gland size were taken as

- 40-60 mm longitudinal diameter
- 13-18 mm AP diameter
- thyroid volume (excluding isthmus, unless its thickness is >3 mm) are 10-15 ml for females and 12-18 ml for males)[9].

CFDUS was performed by a single radiologist using a 5-12 MHz transducer attached Medison Sonoace X8 USG doppler machine and the findings were assessed in 4 grades[1] :

(1) absent intraparenchymal vascularity or minimal spots

(2) presence of parenchymal blood flow with patchy, uneven distribution

(3) mild increase in color flow doppler signal with patchy distribution

(4) markedly increased color flow doppler signal with diffuse homogenous distribution which is also called "thyroid inferno[8]."

Grades 1 and 2 were considered as low or normal vascularity and grades 3 and 4 were considered as a hypervascular thyroid gland. PSV of both left and right ITAs were assessed and their mean flows were calculated and considered as study variables.

The data obtained from the participants were expressed as mean± standard deviation and comparison of means between the groups were done by 't' test. Non parametric data were compared with "Chi-square" test and "Fisher's exact" test. SPSS 21 was used for analysis of collected data. A p value of less than 0.05 was considered as significant. Ethical approval was obtained from the Research Ethics Board of the institute before this study was undertaken.

## Results

This study included 57 patients who presented with features of thyrotoxicosis. Out of 21 patients were included in the GD group and the rest 36 were in the SAT group. The mean age of the patients in GD group was 37.86±11.59 years and in SAT group was 36.58±9.711 years (p=0.658) which mostly reflects the thyroid disturbance in young to middle aged people. Female predominance was seen in our study as 45(78.94%) among 57 participants were female. When we compared the symptoms of thyrotoxicosis obtained from history between the two groups it was observed that except sore-throat and antecedent fever most of the symptoms were found to be more frequent in the GD group especially the eye related ones (Table 1). Signs of thyrotoxicosis such as tremor, restlessness and muscle weakness were more frequently found in the patients of GD group (Table 2).

ESR was significantly higher in the SAT group and there were not much difference seen with other parameters like haemoglobin, TLC and thyroid function (Table 3). Prevalence of goiter and hypoechogeneicity of the gland on gray scale sonography did not differ between the groups. There is significant increase in the level of vascularity in the patients of GD group. One of them showed the "thyroid inferno" pattern. Left Inferior Thyroid Artery PSV was significantly higher in the GD group with a mean value of around 56 cm/sec compared to a mean of around 26cm/sec in SAT (Table 4).

Table 1 — *Showing comparison of thyrotoxic symptoms among two groups*

| Symptoms | Graves' Disease | Subacute Thyroiditis | p-value |
|---|---|---|---|
| Sore- throat | 4 (19.0%) | 12 (33.3%) | 0.247 |
| Antecedent fever | 3 (14.3%) | 18 (50.0%) | 0.007 |
| Tremor | 18 (85.7%) | 14 (38.9%) | 0.001 |
| Palpitation | 17 (81.0%) | 19 (52.8%) | 0.033 |
| Weight loss | 15 (71.4%) | 17 (47.5%) | 0.123 |
| Heat intolerance | 8 (38.1%) | 10 (27.8%) | 0.419 |
| Hyper defaecation | 3 (14.3%) | 6 (16.7%) | 0.564* |
| Increased appetite | 8 (38.1%) | 3 (8.3%) | 0.012* |
| Neck swelling | 11 (52.4%) | 15 (41.7%) | 0.433 |
| Foreign body sensation | 3 (14.3%) | 1 (2.8%) | 0.136* |
| Double vision | 2 (9.5%) | 0 (0.0%) | 0.132* |
| Prominace of eyes | 3 (14.3%) | 0 (0.0%) | 0.045* |
| Diminished vision | 1 (4.8%) | 3 (8.3%) | 0.529* |
| Family History | 2 (9.5%) | 4 (11.1%) | 0.613* |

*Analysis done using Chi-square and *Fisher's exact test*

Table 2 — *Showing the comparison of thyrotoxic signs between two groups*

| Signs | Graves' Disease | Sub acute Thyroiditis | p-value |
|---|---|---|---|
| Tremors | 17 (81.0%) | 14 (38.9%) | 0.002 |
| Restlessness | 12 (57.1%) | 4 (11.1%) | 0.000 |
| Muscle weakness | 7 (33.3%) | 0 (0.0%) | 0.000* |
| Goitre | 13 (61.9%) | 16 (44.4%) | 0.203 |
| Onycholysis | 3 (14.3%) | 1(2.8%) | 0.136* |
| Ophthalmopathy | 2 (9.5%) | 0 (0.0%) | 0.132* |

*Analysis done using Chi-square and *Fisher's exact test*

Table 3 — *Comparison of the haematological investigations between two groups*

| Blood Tests | Graves' Disease (mean±SD) n=21 | Subacute Thyroiditis (mean±SD) n=36 | p-value |
|---|---|---|---|
| Haemoglobin (gm/dL) | 12.48±1.537 | 12.68±1.414 | 0.607 |
| TLC | 6828.57±1816.079 | 7711.94±2829.153 | 0.205 |
| ESR (mm/1st hour) | 21.05±27.198 | 50.53±20.031 | 0.000 |
| TSH (mIU/L) | 0.1126±0.30349 | 0.0406±0.07087 | 0.176 |
| T3 (nmol/L) | 7.00±2.911 | 6.09±3.752 | 0.346 |
| T4 (nmol/L) | 278.14±64.673 | 261.86±77.172 | 0.419 |

*TLC – total leucocyte count ; ESR – erythrocyte sedimentation count*
*TSH – thyroid stimulating hormone ; Analysis done using student 't' test*

Table 4 — *Showing comparison of ultrasound findings between the two groups*

| Ultrasound Findings | Graves' Disease | Sub-acute Thyroiditis | p-value |
|---|---|---|---|
| Enlargement | 16 (76.2%) | 19 (56.8%) | 0.080 |
| Hypoechogenicity | 18 (85.7%) | 34 (94.4%) | 0.346* |
| Increased vascularity | 16 (76.2%) | 9 (25.0%) | 0.000 |
| Right ITA PSV (mean±SD) (cm/sec) | 45.67±22.223 | 25.77±32.716 | 0.197 |
| Left ITA PSV (mean±SD) (cm/sec) | 56.17±21.575 | 25.77±23.474 | 0.016 |

*ITA – inferior thyroid artery ; PSV- peak systolic velocity*
*Analysis done using students 't'test and Chi-square test*

## Discussion

Thyrotoxicosis with diffuse thyroid disease is either caused by hyperfunction of thyroid gland such as GD or destructive like silent thyroiditis, SAT, and postpartum thyroiditis. Differentiation of these two types of thyrotoxicosis is very important as patients with GD must be treated with antithyroid drugs, radioiodine therapy or subtotal thyroidectomy, while patients with destructive thyrotoxicosis are treated with conservative therapy[1,3].

Among the causes of spontaneous thyrotoxicosis, GD is the commonest[2]. Typical cases of GD, ie, those with ophthalmopathy and skin and nail changes are not very difficult to diagnose. But differentiation of destructive thyroiditis and early GD is very challenging. Radio active iodine uptake (RAIU) has been considered as the traditional diagnostic approach in common practice for differentiation of GD related and non Graves' disease related thyrotoxicosis but limited availability in our parts of our country and contraindication in pregnancy, lactation makes the diagnosis real difficult sometimes[3].

Our study included 57 patients, 21 with Graves' disease and 36 with subacute thyroiditis among whom we can clearly see a female predominace. Almost 80% of our participants were female which is similar with the study conducted by Harikumar *et al*[1]. And the female predominance is even more in the SAT group. Similar findings were also seen in the study of Harikumar *et al*[1] where the percentage of female patients in GD and thyroiditis groups were 70.58% and 87.10% respectively.

History of sore throat and antecedent fever is more in the SAT group which suggests an eminent role of a recent viral infection as an etiological factor in SAT as suggested by Volpe *et al*[10]. Thyrotoxic symptoms like tremors and palpitations were significantly higher in GD group. Almost half of the patients in each group have complained about having neck swelling but symptoms related to eyes were more frequent with patients in GD group.

Patients with GD had significantly higher pulse rate than those with SAT though tachycardia is present is present in SAT also. Similarly tremor was also found to be present more frequently in GD group. Other findings like restlessness, muscle weakness were also significantly higher in GD. Ophthalmopathy was present only in GD patients. Though goitre was seem to be more prevalent in GD group but it was statistically insignificant. Thyroid profile showed no difference between the group.

Among the haematological parameters, ESR was significantly higher in the SAT group which support the presence of an acute inflammatory process behind the thyrotoxicosis in SAT.

Gray-scale ultrasonography (USG) is the basic modality in the examination of thyroid gland. Echogenicity of the thyroid is a qualitative ultrasound variable that has been evaluated as an index of the relapsing or remitting course of the disease[11]. It usually shows an enlarged gland with a pronounced hypoechoic pattern in patients with GD. This hypoechoic pattern is the reflection of infiltration by lymphocytes and follicular degeneration of the gland which is a better marker than thyroid antibodies for predicting thyroid dysfunction[12].

On grayscale ultrasonography, thyroid gland was found to be enlarged in more than half of the participants and among them the frequency was higher in the patients with GD. In the GD group, 76.2% of participants had an enlarged thyroid.

Echogenicity of thyroid in gray scale ultrasonography hypoechogenicity was seen more in the participants of SAT group. Alzahrani *et al*[2] have found out in their study that most of the cases of Graves' disease showed hypoechogenicity though it was not specific for the disease but more specific for thyroiditis especially Hashimoto's thyroiditis.

Doppler ultrasonography is a powerful imaging technique which not only identifies a substantial proportion of patients with GD but also can be used to assess the disease activity and predicts the outcome after withdrawal of medical therapy[13]. The advantage of CFDUS is that it allows visualization of the blood flow in the examined tissue and thus provides a very important tool for the diagnosis of GD which is characterized by a marked, diffuse increase in intrathyroidal blood flow as observed by Sponza *et al*[14], Kumar KV *et al*[15], Bogazzi *et al*[16] and Aldasouqi *et al*[17] CFDUS showed a significantly increased level of vascularity in patients with GD. During the assessment of thyroid function we saw that the TSH and T4 level higher in the SAT group which was not expected. Inspite of this contrasting result, GD group has shown significantly increased vascularity which perfectly matches with the findings of Bogazzi *et al*[18], Arslan *et al*[19] and Baldini *et al*[20] who have shown that there was no relationship of vascularity and severity of disease and the hypervascularism was not related to the circulating thyroid hormone levels but probably related to the activity of underlying autoimmune process.

In that context, another study worth a mention is the one conducted by Kurita *et al*[21]. They measured the Thyroid Blood Flow Area which was a quantitative measurement of area showing thyroid blood flow calculated as a percentage of total thyroid area and they have established it as a moderately effective method to distinguish between GD and thyroiditis. In their study, 95% of GD patients had TBFA of 8% which was sufficient to distinguish it from destructive thyroiditis.

Hiromatsu *et al*[6] have shown hypoechoic swollen thyroid without increased tissue vascularity as a feature of subacute thyroiditis. But he also mentioned about findings of slightly increased vascularity in the patients with SAT in recovery stage which was well correlated with thyroid hormone levels and normalized within 1 year of follow up.

Peak systolic velocity of left inferior thyroid arteries was significantly higher in patients of GD group. In 1999, Caruso *et al*[22] performed doppler ultrasound of thyroid and measured the inferior thyroid artery PSV in 8 patients of GD and 23 patients of throiditis for 8 months and showed that the mean PSV of ITA was always more than 150cm/s in GD patients and never more than 65cm/s in thyroiditis patients. In 2013, Banaka *et al*[23] showed that the specificity of left ITA PSV was 91.7% and established a reference range of 26.11cm/s. The Youden index of left ITA PSV (0.697) was much higher than right ITA PSV in his study. Vitti *et al*[24] studied the thyroid blood flow by CFDUS and PSV in ITA in 37 GD and 45 goitrous Hashimoto's thyroiditis patients and observed similar results.

Harikumar *et al*[1] found an ITA PSV of 57.6±13.1 cm/s (p=0.05) in GD which is comparable with our study. Their ITA PSV of 22.4±5.6 was also similar to our findings. Erdogan *et al*[15] conducted a study with 29 patients of Graves' Disease, 26 Toxic Adenoma patients, 24 Hashimoto's Thyroiditis patients and 39 euthyroid patients as control in which they found higher intrathyroidal vascularity in Graves' Disease.

There are some limitations of the present study which include small sample size, no assay for Anti-thyroperoxidase antibodies (Anti-TPOAb) which are present in around 80% cases of GD[25] so its absence does not exclude GD. And it can be present in around 10% of normal individuals. Finally, Radio-iodine uptake was not done as this facility is not available in our state.

## Conclusion

In centers with no facility for Radio-iodine uptake test, doppler ultrasonography assessing the peak systolic velocity of inferior thyroid artery can be used as an alernative method to differentiate GD from SAT where history, physical examination and other laboratory investigation may not give a definitive clue.

## References


1 Hari Kumar KV, Vamsikrishna P, Muthukrishnan J, Verma A, Rayudu BR, Modi KD — Role of thyroid doppler in differential diagnosis of thyrotoxicosis. *Endocr Pract* 2009; **15:** 6-9.

2 Alzahrani AS, Ceresini G, Aldasouqi SA — Role of ultrasonography in the differential diagnosis of thyrotoxicosis: A noninvasive, cost-effective, and widely available but underutilized diagnostic tool. *Endocr Pract* 2012; **18:** 567-8.

3 Ota H, Amino N, Morita S, Kobayashi K, Kubota S, Fukata S, et al. Quantitative measurement of thyroid blood flow for differentiation of painless thyroiditis from Graves' disease. *Clin Endocrinol* 2007; **67:** 41-5.

4 Uchida T, Shigihara N, Takeno K, Komiya K, Goto H, Abe H, *et al* — Characteristics of patients with Graves disease and intrathyroid hypovascularity compared to painless thyroiditis. *J Ultrasound Med* 2014; **33:** 1791-6.

5 Ishay A, Pollak Y, Chervinsky L, Lavi I, Luboshitzky R — Color-flow doppler sonography in patients with subclinical thyroid dysfunction. *Endocr Pract* 2010; **16:** 376-81.

6 Hiromatsu Y, Ishibashi M, Miyake I, Soyejima E, Yamashita K, Koike N, *et al* — Color doppler ultrasonography in patients with subacute thyroiditis. *Thyroid* 1999; **9:** 1189-93.

7 Erdogan MF, Anil C, Cesur M, Baskal N, Erdogan G — Color flow doppler sonography for the etiologic diagnosis of hyperthyroidism. *Thyroid* 2007; **17:** 223-8.

8 Ralls PW, Mayekawa DS, Lee KP, Colletti PM, Radin DR, Boswell WD, *et al* — Color-flow doppler sonography in Graves' disease: "Thyroid Inferno—". *Am J Roentgenol* 1988; **150:** 781-4.

9 Choudhary V, Bano S — Thyroid ultrasound. *Indian J Endocr Metab* 2013; **17:** 219-27.

10 Volpe R, Row VV, Ezrin C — Circulating viral and thyroid antibodies in subacute thyroiditis. *J Clin Endocrinol Metab* 1967; **27:** 1275-84.

11 Baldini M, Orsatti A, Bonfanti MT, Castagnone D, Cantalamessa L — Relationship between the sonographic appearance of the thyroid and the clinical course and autoimmune activity of Graves' disease. *J Clin Ultrasound* 2005; **33:** 381-5.

12 Rago T, Chiovato L,Grasso L, Pinchera A, Vitti P — Thyroid ultrasonography as a tool for detecting thyroid autoimmune diseases and predicting thyroid dysfunction in apparently healthy subjects. *J Endocrinol Invest* 2001; **24:** 763-9.

13 Castagnone D, Rivolta R, Rescalli S, Baldini MI, Tozzi R, Cantalamessa L — Color doppler sonography in Graves' disease: Value in assessing activity of disease and predicting outcome. *Am J Roentgenol* 1996; **66:** 203-7.

14 Sponza M, Fabris B, Bertolotto M, Ricci C, Armini L — Role of doppler color ultrasonography and of flowmetric analysis in the diagnosis and follow-up of Grave's disease [article in Italian]. *Radiol Med* 1997; **93:** 405-9.

15 Kumar KV, Vamsikrishna P, Verma A, Muthukrishnan J, Rayudu BR, Modi KD — Utility of colour doppler sonography in patients with Graves' disease. *West Indian Med J* 2009; **58:** 566-70.

16 Bogazzi F, Vitti P — Could improved ultrasound and power doppler replace thyroidal radioiodine uptake to assess thyroid disease? *Nat Clin Pract Endocrinol Metab* 2008; **4:** 70-1.

17 Aldasouqi S, Sheikh A, Klosterman P — Doppler ultrasonography in the diagnosis of Graves' disease: a non-invasive, widely under-utilized diagnostic tool. *Ann Saudi Med* 2009; **29:** 323-4.

18 Bogazzi F, Bartalena L, Brogioni S, Burelli A, Manetti L, Tanda ML — Thyroid vascularity and blood flow are not dependent on serum thyroid hormone levels: studies in vivo by color flow doppler sonography. *Eur J Endocrinol* 1999; **140:** 452-6.


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19 Arslan H, Unal O, Algu¨n E, Harman M, Sakarya ME — Power doppler sonography in the diagnosis of Graves' disease. *Eur J Ultrasound* 2000; **11:** 117-22.

20 Baldini M, Castagnone D, Rivolta R, Meroni L, Pappalettera M, Cantalamessa L — Thyroid vascularization by color doppler ultrasonography in Graves' disease. Changes related to different phases and to the long-term outcome of the disease. *Thyroid* 1997; **7:** 823-8.

21 Kurita S, Sakurai M, Kita Y, Ota T, Ando H, Kaneko S, Takamura T, *et al* — Measurement of thyroid blood flow area is useful for diagnosing the cause of thyrotoxicosis. *Thyroid* 2005; **15:** 1249-52.

22 Caruso G, Attard M, Caronia A, Lagalla R — Color Doppler measurement of blood flow in the inferior thyroid artery in patients with autoimmune thyroid diseases. *Eur J Radiol* 2000; **36:** 5-10.

23 Banaka I, Thomas D, Kaltsas G — Value of the left inferior thyroid artery peak systolic velocity in diagnosing autoimmune thyroid disease. *J Ultrasound Med* 2013; **32:** 1969-78.

24 Vitti P, Rago T, Mazzeo S, Brogioni S, Lampis M, De Liperi A, *et al* — Thyroid blood flow evaluation by color-flow doppler sonography distinguishes Graves' disease from Hashimoto's thyroiditis. *J Endocrinol Invest* 1995; **18:** 857-61.

25 Feldt-Rasmussen U, Hoier-Madsen M, Bech K, Blichert-Toft M, Bliddal H, Date J, *et al* — Anti-thyroid peroxidase antibodies in thyroid disorders and non-thyroid autoimmune diseases. *Autoimmunity* 1991; **9:** 245-54.