Utility of Colour Doppler Sonography in Patients with Graves' Disease

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ABSTRACT

Objective: *Assessment of thyroid blood flow gives valuable information about underlying functional status. Colour Flow Doppler Sonography (CFDS) is a powerful tool which displays tissue blood flow and vascularity. Colour Flow Doppler Sonography of the thyroid gland in different subsets of patients with Graves' disease was studied to define its role in initial diagnosis and management.*

Methods*: Eighty consecutive patients with Graves' disease (both treated and untreated) presented to hospital between August 2007 and February 2008. All patients were evaluated with CFDS of the thyroid for size, vascularity and peak systolic velocity (PSV) of the Inferior Thyroid Artery (ITA). Pertechnate scan and thyroidal autoantibody levels were done in selected cases. The patients were divided into Untreated Graves' disease (n = 31), Graves' disease on treatment but hyperthyroid (n = 26) and euthyroid Graves' disease on therapy (n = 23). Mann-Whitney U-test was used for statistical analysis and a* p*-value of less than 0.05 was considered significant.*

Results: *Thyroid blood flow, as assessed by PSV of ITA, was significantly higher in untreated Graves' disease than in Graves disease on treatment but hyperthyroid and euthyroid Graves respectively (61.5 ± 19.5* versus *42.9 ± 24.7* versus *32.2 ± 12.9 cm/s,* $p < 0.05$*). Parenchymal vascularity of the thyroid gland was higher in hyperthyroid patients than in euthyroid patients irrespective of therapy. In both groups on therapy, the dose of carbimazole correlated with the vascularity of the gland (r = 0.492* versus *0.564,* $p < 0.05$*). Colour Flow Doppler Sonography parameters correlated significantly with pertechnate scan results giving comparable sensitivity and specificity.*

Conclusion: *Assessment of thyroid blood flow by CFDS is an effective marker in the initial diagnosis of Graves' disease. Vascularity of the gland can predict long term disease course while on medical therapy.*

Utilidad de la Sonografía Doppler en Color en Pacientes con la Enfermedad de Graves

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RESUMEN

Objetivo: *La evaluación del flujo sanguíneo tiroideo ofrece una valiosa información acerca del estatus funcional subyacente. La sonografía del flujo con Doppler a color (CFDS) es un poderoso instrumento que muestra el flujo del tejido sanguíneo y la vascularidad. La sonografía con Doppler a color, de la glándula tiroides en diferentes subconjuntos de pacientes con la enfermedad de Graves, fue estudiada para definir su papel en el diagnóstico inicial y el tratamiento.*

Métodos: *Ochenta pacientes consecutivos con la enfermedad de Graves (con y sin tratamiento) acudieron al hospital entre agosto de 2007 y febrero de 2008. Mediante CFDS, a todos los pacientes les fueron evaluados el tamaño del tiroides, la vascularidad y la velocidad del pico sistólico (PSV) de la arteria tiroidea inferior (ATI). En casos seleccionados, se realizaron gammagrafías con pertecnetato y estudios de los niveles de anticuerpos tiroideos. Los pacientes fueron clasificados tomando como criterios: la enfermedad de Graves sin tratamiento (n = 31), la enfermedad de Graves con tratamiento pero hipertiroideos (n = 26), y la enfermedad de Graves eutiroidea bajo terapia (n = 23). La prueba U de Mann-Whitney fue utilizada para el análisis estadístico, y un valor p menor de 0.05 fue considerado significativo.*

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Resultados: *El flujo sanguíneo tiroideo tal cual fue evaluado mediante PSV de ATI, fue significativamente más alto en la enfermedad de Graves sin tratamiento que en otros grupos (61.5 ± 19.5* versus *42.9 ± 24.7* versus *32.2 ± 12.9 cm/s,* p < *0.05). La vascularidad parenquimal de la glándula tiroides fue mayor en los pacientes hipertiroideos, independientemente de la terapia. En los dos grupos bajo terapia, las dosis de carbimazol estaban en correlación con la vascularidad de la glándula (r = 0.492* versus *0.564,* p < *0.05). Los parámetros de la sonografía del flujo con Doppler a color guardaban una correlación significativa con los resultados de la gammagrafía de pertecnetato, arrojando sensibilidad y especificidad comparables.*

Conclusión: *La evaluación del flujo sanguíneo del tiroides mediante CFDS es un marcador efectivo en el diagnóstico inicial de la enfermedad de Graves. La vascularidad de la glándula puede predecir el curso de la enfermedad a largo plazo, bajo terapia médica.*

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INTRODUCTION

Graves' disease (GD) is a chronic, autoimmune, diffuse thyroid disease characterized by markedly increased blood flow of the gland (1). Increased thyroidal blood flow is seen to be correlated with iodine uptake and thyroid hormone levels (2, 3). Graves' disease patients can have a stable remission after medical therapy or can have relapsing and unremitting course. The practical issues of concern in management of Graves' disease patients are differentiating early GD from destructive thyrotoxicosis and predicting remission of disease. ^{99m}Tc pertechnate scan and TSH receptor antibody levels help in aetiological differentiation of thyrotoxicosis in difficult situations (4). However, these methods are time consuming and not available widely thus limiting their use. Various factors like gland size, autoantibody titre, antithyroid drug requirement are used to predict remission of GD (5). But, none of these markers reliably predicts the course of the disease and guide decisions regarding ablative therapy.

Ultrasonography is a very informative tool and colour doppler gives an additional advantage of directly measuring the tissue vascularity (6). Colour Flow Doppler Sonography of the thyroid gland helps in assessing thyroid gland functional status indirectly by studying the vascularity (7). The evaluation is both qualitative (visual impression of thyroid vascularity) and quantitative (flow velocity in intrathyroidal and ITA). Thus, CFDS of the thyroid gland is proposed to be useful in initial diagnosis and in predicting remission in patients with Graves' disease (8–10). Colour Flow Doppler Sonography of the thyroid was studied in various stages of patients with Graves' disease and its role was analyzed in the initial diagnosis and course of the disease.

SUBJECT AND METHODS

Eighty consecutive patients with Graves' disease at different phases of disease were studied between August 2007 and February 2008. A detailed history was taken regarding palpitations, weight loss, ophthalmic complaints and past history of similar illness or family history of thyroid illness. The radial pulse, blood pressure and pulse pressure were recorded. Ophthalmopathy, skin and nail changes related to hyperthyroidism, goitre and thyroid bruit were carefully looked for. Thyroid function tests were done in all patients but ^{99m}Tc pertechnate scan and thyroid peroxidase antibody was advised in selected cases when diagnosis was doubtful. Patients with past history of thyroid surgery or exposure to radioiodine therapy were excluded from the study. Graves' disease was diagnosed when thyrotoxicosis was associated with clinical features like weight loss or poor weight gain, palpitations, goitre, ophthalmopathy (more than Class 2 NOSPECS classification), T3/T4 ratio > 20 and increased uptake on pertechnate scan (11, 12). The patients were subdivided into three groups for analysis: Group A – untreated Graves' disease (n = 31); Group B – treated Graves' disease but hyperthyroid (n = 26), Group C – Graves' disease, euthyroid on therapy (n = 23).

Colour Flow Doppler Sonography of the thyroid gland was done in all patients by the same radiologist using ultrasound digital equipment (Philips® Envisor machine) in connection with 7.5-MHz linear transducer. Various parameters like size, gland vascularity and peak systolic velocity (PSV) of ITA were assessed. Thyroid volume was calculated using maximum width (W), thickness (T), length (L) of right (r) and left (l) lobes using the equation: (WrTrLr + WlTlLl) X 0.7 (13). Gland vascularity was graded into 4 grades as per the patterns described: Grade 1: absent intraparenchymal vascularity or minimal spots; Grade 2: presence of parenchymal blood flow with patchy uneven distribution; Grade 3: mild increase of colour flow doppler signal with patchy distribution; Grade 4: markedly increased colour flow doppler signal with diffuse homogeneous distribution, the 'thyroid inferno' pattern (7, 14). The ITA was selected for doppler study and flow in the thyroid artery was reported in centimetres per second from Doppler spectrum time averaged mean velocity and vessel diameter. The doppler angle of insonation was corrected to 60° or less. Two calipers were positioned on the internal walls of the arteries to calculate the vessel diameter on the gray scale image. There was no significant difference between the PSV of inferior

thyroid artery from both sides of the thyroid gland (Data not shown). Hence arithmetic mean derived from both values was taken in this study.

Summary data are expressed as mean ± SD and comparison between groups was done by Mann-Whitney U-test. The relationship between thyroidal vascularity and other parameters was done by Pearson's linear correlation analysis. A probability value of less than 0.05 was considered to be statistically significant.

RESULTS

The clinical, biochemical and sonologic data of the patients are summarized in Table 1. The PSV of ITA of all patients is shown in Fig. 1. Patients with hyperthyroidism as a group had higher PSV values than euthyroid patients on therapy.

Table 1: Clinical, biochemical and sonologic parameters in patients with Graves' Disease

	Group A (Untreated)	Group B (Hyperthyroid on therapy)	Group C (Euthyroid on therapy)
Number	31	26	23
Sex (M/F)	4/27	6/20	5/18
Age (years)	37.3 ± 13.2	35.9 ± 10.5	42.8 ± 11.6
Duration of disease (months)	–	27.8 ± 13.5	43.2 ± 36.3
Carbimazole dose (mg)	–	28.9 ± 14.9	28.9 ± 14.9
TSH (µIU/ml)	0.03 ± 0.08	0.08 ± 0.1	6 ± 9.3
Thyroid volume (cc)	26.7 ± 11.1	28.9 ± 14.9	28.2 ± 8.8
Vascularity (Grade)	3.4 ± 0.6	2.8 ± 0.8	2.3 ± 0.9
PSV (cm/sec)	61.5 ± 19.5	42.9 ± 24.7	32.2 ± 12.9

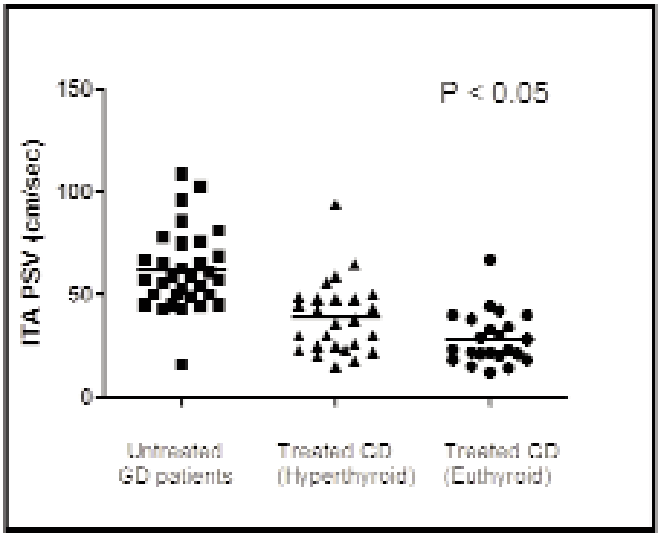
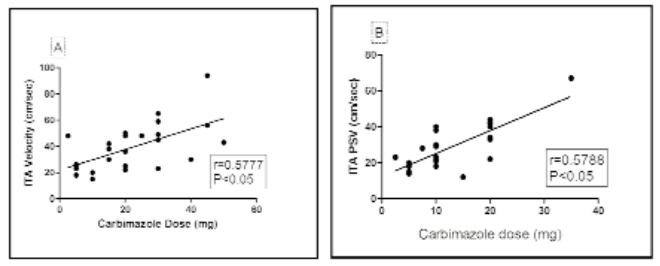


Fig. 1: The peak systolic velocity of the inferior thyroid artery of patients with Graves' disease.

Treated patients with GD but still hyperthyroid, showed a significantly higher vascularity than euthyroid GD patients on therapy. Pertechnate scan was done for 14 out of 31 patients in untreated GD patients and all had shown increased uptake. All these patients had corresponding elevated Doppler vascular parameters except in a case of apathetic thyrotoxicosis. Dose of antithyroid drug showed linear correlation with the underlying vascularity in both groups on therapy (Fig. 2A, 2B).



A B

Fig. 2: Correlation between peak systolic velocity of inferior thyroid artery and antithyroid drug dose in patients with Graves' disease on therapy; A: Uncontrolled (Hyperthyroid) and B: Controlled (Euthyroid).

DISCUSSION

Untreated patients with Graves' disease had hypervascularity of the gland as demonstrated by increased parenchymal vascularity and PSV of ITA. Ota *et al* and other authors also reported similar findings of increased blood flow in untreated hyperthyroidism (8, 15, 16). In the present study, pertechnate scan findings correlated well with CFDS findings of increased blood flow except in a patient of apathetic thyrotoxicosis for unclear reasons. Kurita *et al* after studying 75 patients with thyrotoxicosis gave a sensitivity of 84% and specificity of 90% for CFDS in the diagnosis of thyrotoxicosis (17). The present study showed a similar sensitivity and specificity. Thus, CFDS findings were comparable to nuclear imaging (sensitivity 90% and specificity 90%) in the diagnosis of GD. The sensitivity of CFDS is further improved with newer methods like high resolution power doppler for better aetiological differentiation (18). Hence, CFDS could be helpful in the initial evaluation of thyrotoxicosis of various aetiologies and may avoid nuclear imaging in a substantial number of patients (9, 17, 19).

Thyroid vascularity was significantly higher in patients with uncontrolled disease when compared to euthyroid patients on antithyroid drugs Mean Grade of Vascularity (2.8 ± 0.8 *versus* 2.3 ± 0.9, $p < 0.05$). Thus the vascularity of the thyroid gland correlates with the underlying functional status and decreases with disease under control. Ralls *et al* studied patients with GD prospectively and observed that vascularity remission occurred in parallel to biochemical remission and disease control (14, 20). They proposed that CFDS has potential to monitor therapeutic response in GD patients without expensive laboratory tests. Data from the index report showed a linear correlation between antithyroid drug dose and vascularity of the gland (r = 0.5777 and 0.5788, $p < 0.05$) in both groups on therapy. Saleh *et al* showed a similar

result in which colour pixel density measurements could be useful to estimate the antithyroid drug dose (21). Therefore, to summarize, CFDS parameters correlate well with underlying disease activity and drug requirement. However, Baldini *et al* in their study demons-trated that thyroid vascularity is related more to the under-lying autoimmunity than the circulating thyroid hormone levels in euthyroid patients on therapy (22). We could not analyse the relation of thyroid vascularity with TSH receptor antibody levels as the latter result is not available.

Recommendations regarding the therapeutic strategy between prolonged ATD use and ablative therapy have not been standardized. The likelihood of long term remission after medical treatment cannot be predicted reliably with available parameters (5). In the present study population, four patients with long standing disease (more than one year) were advised to stop antithyroid drugs after clinical and biochemical euthyroidism. Out of them, two had early relapse of the disease (less than three months) and these two patients had significantly higher vascularity of the gland in comparison to the remaining two patients at the time of drug withdrawal (data not shown). This preliminary data suggest that quantification of TBF by means of CFDS might be a useful tool to predict the outcome of Graves' disease following withdrawal of medical treatment and could be helpful in recommending suitable therapy. Wang *et al* studied the role of ultrasonography prior to ablative therapy recommendation and proposed that resistive index coupled with TSH value could be helpful in proper selection (23).

The limitations of this study are that the results of nuclear imaging and thyroid antibodies were not available for all patients as we performed them in selected cases only. Diagnosis of Graves' disease was not confirmed with TSH stimulating antibody level, as this test is not widely available in our country. The study did not include patients in prolonged clinical remission not using antithyroid drug. Inclusion of these patients could have helped in further defining the role of CFDS. Thyroid ultrasound examination is operator dependent but in this study a single radiologist performed ultrasonography on all patients.

In summary, the flow is a useful marker in initial diagnosis of Graves' disease. The high correlation between radioisotope scan and CFDS establishes this modality as an acceptable alternative. Its role in pregnancy and lactation where nuclear imaging is contraindicated needs to be emphasized. Preliminary data show the role of CFDS in monitoring patients with GD on antithyroid drug therapy and helps in selection for ablative therapy. We recommend CFDS evaluation of the thyroid gland as an essential part in management of Graves' disease patients.

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