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ROLE OF PEAK SYSTOLIC VELOCITY OF INFERIOR THYROID ARTERY IN DIFFERENTIAL DIAGNOSIS OF GRAVES' DISEASE AND HASHIMOTO'S THYROIDITIS

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ABSTRACT

Background: Thyrotoxicosis is the clinical manifestation of a set of illnesses defined by excessive thyroid hormone action at the tissue level, as a result of excessive thyroid hormone concentrations. **The aim of the study:** The aim of this study was to evaluate the diagnostic value of ITA-mPSV in differentiating of thyrotoxicosis among Iraqi population. **Patients and Methods:** From the total 50 cases; 25 patients with proved diagnosis of thyrotoxicosis and 25 patients with thyroiditis were examined in the sonography unit of Rizgary Teaching Hospital, clinical history was taken and physical examination and thyroid function tests were performed for all patients. **Results:** Thyrotoxicosis patients are younger than thyroiditis patients, but the difference is statistically insignificant. Thyroid volume in thyrotoxicosis (22.14±7.56) is statistically significant higher than thyroiditis (11.92± 4.68). The systolic-diastolic ratio and resistive index of the study groups do not differ significantly. At the cut-off point of (61.50 cm/s); the sensitivity is 96.0%, while the specificity is 92.0%. Positive and negative predictive values are 92.3% and 95.8% respectively with the AUC is (0.962). **Conclusion:** Measurement of peak systolic velocity of inferior thyroid artery is a useful diagnostic tool for distinguishing between GD and thyroiditis, with high sensitivity and specificity.

1. INTRODUCTION

1.1. Overview

Thyrotoxicosis is the clinical manifestation of a set of illnesses defined by excessive thyroid hormone action at the tissue level, as a result of excessive thyroid hormone concentrations.[1] While Hashimoto thyroiditis which known also known as chronic autoimmune thyroiditis and chronic lymphocytic thyroiditis, is an autoimmune disease in which thyroid cells are destroyed via cell and antibody-mediated immune processes. It is the most common cause of hypothyroidism in developed countries.[2]

Thyrotoxicosis is a medical condition in which the thyroid gland produces and secretes too much thyroid hormone.

There are two types of thyrotoxicosis: overt and subclinical. Low serum thyroid-stimulating hormone (TSH) concentrations and elevated serum concentrations of thyroid hormones: thyroxine (T4), triiodothyronine (T3), or both, characterize overt thyrotoxicosis. Low serum TSH but normal serum T4 and T3 concentrations characterize the subclinical thyrotoxicosis.[3]

1.2. Epidemiology

Thyrotoxicosis affects 8% of people in Europe and 13% of people in the United States of America. Thyrotoxicosis is more common in women and increases with age (20-50years) Overt thyrotoxicosis affects 05%–08% of people in Europe and 05% of people in the United States of America. Although there are few data on ethnic differences, thyrotoxicosis appears to be slightly more common among white people than in other races. Mild thyrotoxicosis is also found to be more common in iodine-deficient areas than in iodine-sufficient areas and to have decreased after universal salt iodization programs were implemented.[5, 6]

1.3. Etiology

Thyrotoxicosis is caused by excessive thyroid hormone production from thyroid follicles or by the release or absorption of preformed thyroid hormone at any level of the hypothalamic-pituitary-thyroid axis. Graves' disease (GD) is the most frequent cause of non-iatrogenic thyrotoxicosis in iodine-deficient locations, accounting for 80% of cases, followed by nodular thyroid disease and the thyroiditis.[7]

Graves' disease, toxic multinodular goiter (TMNG), and toxic adenoma (TA) are the most prevalent causes of thyrotoxicosis.[7] Amiodarone and iodinated contrast have been linked to drug-induced thyrotoxicosis. TSH-producing adenomas, struma ovarii, gestational trophoblastic neoplasia, thyrotoxicosis factitia, activation mutations of the TSH receptor, and functional thyroid cancer metastases are all rare causes of thyrotoxicosis.[8] The prevalence of these etiologies, on the other hand, varies with iodine intake (nodular thyroid disease can account for up to 50% of cases in iodine-deficient areas), population age (toxic nodular goiter is more frequent in the elderly), and region investigated (frequency of painless thyroiditis was 0.5% in Denmark vs 22% in Wisconsin.[9, 10]

1.4. Diagnosis

The underlying thyrotoxicosis or immune-mediated cellular infiltration causes the symptoms and signs of GD. Weight loss, weariness, palpitations, tremor, and goiter are the most prevalent symptoms. A palpable goiter is more common in people younger than 60 years.[11]

When there are clinical signs of thyrotoxicosis and biochemical thyrotoxicosis, Graves' disease should be suspected (low serum TSH and high free thyroxine [T4] or triiodothyronine [T3]). Measurement of TSH receptor antibodies (TRAbs) (97% sensitivity and 98%-99% specificity for GD) can be beneficial in the absence of these indications, especially in the case of a nodular goiter.[12]

On the scan, normal or enhanced radioactive iodine (RAI) uptake (RAIU) with diffuse distribution can also confirm the diagnosis and separate GD from other thyrotoxicosis causes as shown in figure (1 and 2). Doppler sonography with thyroid ultrasonography has recently been used to diagnose GD with good accuracy (sensitivity of 87% and specificity of 100).[13]

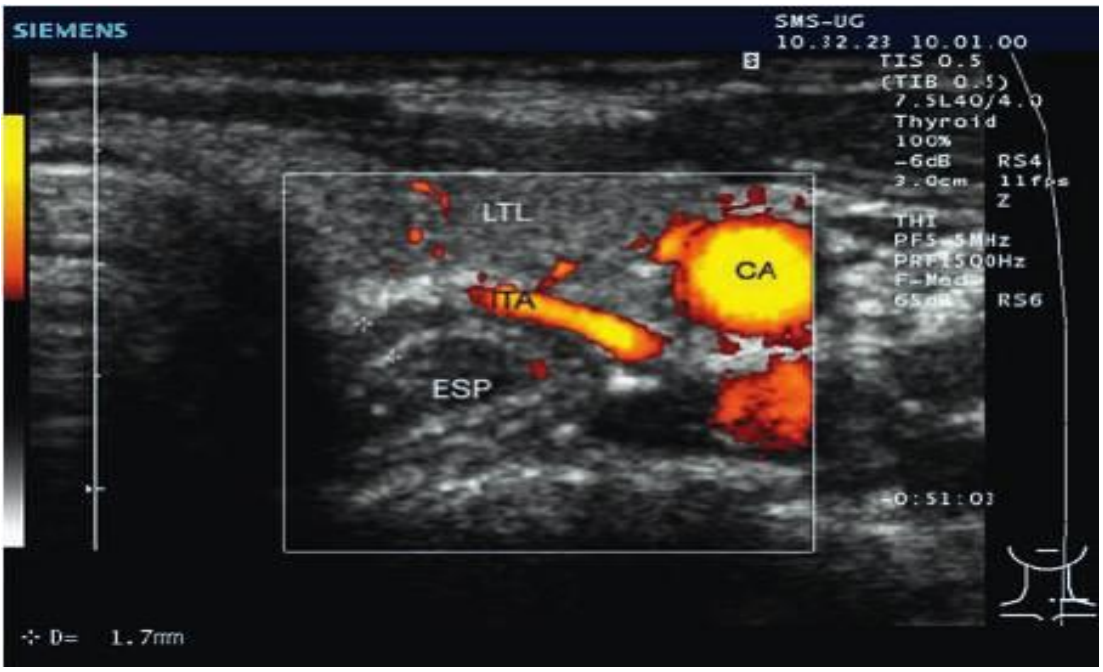


Figure (1): Enhanced radioactive iodine of thyroid gland and ITA.

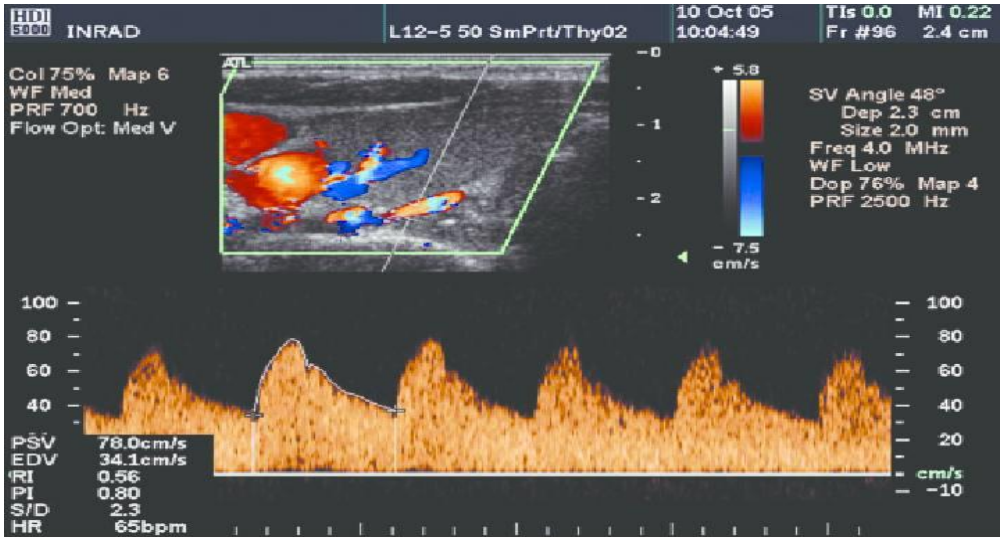


Figure (2): PSV of the ITA.

1.5. Anatomy of ITA and variation

The inferior thyroid artery arises from the thyro-cervical trunk 85% or from the subclavian artery 15% on the pleural dome, in front and a little lateral of the vertebral artery.[14] A case of an inferior thyroid artery (ITA) reported to take its origin directly from the common carotid artery.[15] The inferior thyroid artery) has three segments.[14,15]

1. A proximal segment beginning just outside the vertebral artery.
2. A curved segment that runs medially above the transverse process of C6, passing in front of the vertebral artery and behind the carotid sheath. Here it intersects with the sympathetic cervical chain.
3. Curving again, the artery ascends obliquely in an anteromedial direction. It intersects the lateral border of the esophagus and the trachea, and passes anterior to the recurrent laryngeal nerve (branch of the vagus) on the right and posterior to it on the left.

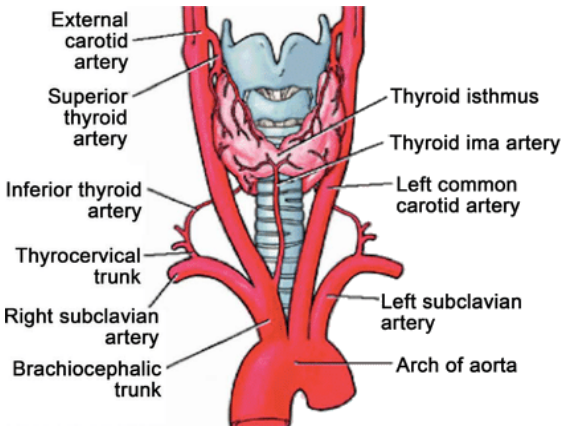
The inferior thyroid artery reaches the posterior surface of the thyroid gland at C5. It winds around the internal jugular vein, common carotid artery, vagus nerve, and sympathetic trunk.[16]

At the level of C5, the inferior thyroid artery passes anterior to the vertebral artery and posterior to the carotid sheath. Manipulation of the inferior thyroid artery at its origin affects the homolateral vertebral artery. The inferior thyroid artery divides into several branches to supply esophagus, trachea, and larynx.[14,16]

The ascending cervical artery is a small branch that arises as the inferior thyroid turns medially behind the carotid sheath. It supplies the adjacent muscles and gives off spinal branches to supply vertebral bodies and the spinal cord, owing to its anastomoses with the spinal arteries. The inferior thyroid artery reaches the thyroid body at the junction of the superior two-thirds and inferior one-third of the gland. It divides into three terminal branches.

1. Inferior laryngeal artery
2. the esophageal artery
3. the tracheal artery
4. the ascending cervical artery
5. pharyngeal artery

An inferior branch anastomoses with its counterpart, along the inferior border of the isthmus.[14] However, part of the scientific literature tends to deny this “classic” origin and shows numerous anatomical variants. Indeed, over the years, several studies (on cadaver models or through non-invasive imaging techniques) and case reports have demonstrated the anatomical variations due to the presence of the abovementioned arteries.[17]



\Figure (3):arterial supply of thyroid gland.

1.6. Treatment

Graves’s disease is treated in two ways: symptom control and treating the underlying thyrotoxicosis. Overstimulation of -adrenergic receptors causes the majority of the symptoms. Blockade is thus the cornerstone of symptom management. Nonselective propranolol also has the added benefit of lowering peripheral T4 to T3 conversion.[6] In the thyroid storm, glucocorticoids are also used for this purpose.[18]

The basic therapeutic choices for the underlying thyrotoxicosis are radioactive iodine ablation, antithyroid medications (ATDs), and thyroidectomy. In the United States (unlike Europe, where ATDs are recommended), radioactive iodine has been the preferred first-line treatment; nevertheless, its use has been declining.[19-21]

Surprisingly, the quality of life after therapy is unaffected by the treatment modality.[22]

1.7. Role of ultrasound and Doppler evaluation of thyroid gland

It's difficult to tell the difference between thyroiditis and early Graves' disease when the signs and symptoms of thyrotoxicosis are not present. However, proper patient management is contingent on a precise diagnosis.[23]

Graves' disease is characterized by diffuse thyroid hypoechogenicity and diffusely increased blood flow on ultrasound. Due to its high sensitivity and ease of use, Doppler has become the first line research in the evaluation of thyroid morphology.[25,26] Doppler study can be used to get a visual picture of thyroid vascularity as well as assess peak systolic, end diastolic, and mean velocities in the inferior thyroid arteries.[26-28]

Furthermore, Doppler distinguishes between Graves' disease (increased blood flow, diffusely enlarged hypoechogenic) and destruction-induced thyrotoxicosis (decreased blood flow). Because nodular goitre is the most common cause of thyrotoxicosis in many European areas, the discrepancies in approach between European and American endocrinologists may be due to the varied epidemiology of thyrotoxicosis.[29] Recently, the measurement of the peak systolic velocity (PSV) of the inferior thyroid artery (ITA) with Doppler ultrasonography was suggested as a sensitive diagnostic tool for the differential diagnosis of thyrotoxicosis.[30]

Several studies have found that measuring thyroid artery blood flow and peak systolic velocity (PSV) can help distinguish thyrotoxicosis from thyroiditis.[31-33] Increased thyroidal artery blood flow and PSV have also been employed as good clinical markers in the diagnosis of thyrotoxicosis, as well as a predictor of disease activity and the recurrence.[34, 35]

Hari Kumar *et al*.[33] investigated the utility of Doppler US for the differential diagnosis of thyrotoxicosis using inferior thyroidal artery (ITA)-mPSV. In thyrotoxicosis patients, the levels of ITA-mPSV were 57.613.1 cm/sec, while in DT patients; the levels were 22.45.4 cm/sec. Furthermore, Caruso *et al*.*[36]* found that in the differential diagnosis of diffuse hyper functional thyroid illness, Doppler blood flow measurement in ITA might overcome the limits of a qualitative intra-parenchymal study.

The purpose of the study: The aim of this study was to evaluate the diagnostic value of ITA-m PSV in differentiating thyrotoxicosis among Iraqi population.

PATIENTS AND METHODS

2.1. Study Design

A hospital based cross-sectional study design was carried out to achieve the aims of the study, we saw a lot of cases with goiter and we exclude others in Erbil city at Rizgary Teaching Hospital over period of six months.

2.2. Ethical Consideration

1. A formal consent had obtained from Arabic Committee for medical specialization and scientific council for medicine of Arabic board.
2. A verbal consent was taken from the patients and the healthy subjects.

2.3. METHOD

From the total 50 cases; 25 patients (20% males and 80% females with proved diagnosis of thyrotoxicosis and 25 patients with hypothyroidism were examined in the sonography unit of Rizgary Teaching Hospital, Data were collected from the patients regarding clinical and physical examination as well as thyroid function test. The sample recruited in the study according to previous clinical diagnosis and lab tests, any individual did not fulfilled the inclusion criteria of being either thyrotoxicosis or thyroiditis was excluded from the study as toxic multi nodular goiter, toxic adenoma, sub acute thyroiditis, auto-immune lymphocytic thyroiditis.

The thyroid glands of all patients were evaluated by Color-flow Doppler ultrasonography of the thyroid tissue was performed by using Philips Ultrasound HD11XE 2011, and spectral flow analysis of inferior thyroid arteries of both sides was assessed. The patients were examined on lying down position with extended neck using linear probe 7Mhz. The Doppler spectral analysis was of the right and left inferior thyroid arteries in the transverse scanning, in which the vessels crossed the common carotid arteries posteriorly, or in the longitudinal scanning of the ascending parts of the arteries, in which the vessels lie parallel to the common carotid arteries. The angle correction cursor was parallel to the direction of flow and the Doppler angle was kept below 60°.

5.4. Statistical Analysis

The data collected during the study were summarized in sheets of Microsoft Excel 2007. The statistical analysis performed by using IBM-SPSS 26. The normality of these data tested by Shapiro-Wilk test, and the parametric tests were decided to be chosen. Means and standard deviations were calculated. The t-test for independent two means used to calculate the difference between two groups. Frequencies were estimated for the nominal data and the Chi square test (x^2) was used with the fissure exact test was used instead when any cell present with expected value less than 5. ROC test was

performed to find the area under curve (AUC) with cut-off point, sensitivity, specificity, positive, and negative predictive values. The AUC indicators were; 1.000-0.900 excellent, 0.900-0.800 good, 0.800-0.700 fair, 0.700-0.600 poor. The p-value ≤ 0.05 considered as significant.

RESULTS

Table (1) demonstrates the demographical characteristics of the sample and reveals that the mean age is 36.90±4.89 years. Only 20.0% of the sample is males and 80.0% is females with male: female ratio of 1:4.

Table (1): The demographical characteristics of the sample.

Demographical characteristics	Mean	Std. Deviation
Age	36.90	4.89
Male: Female ratio	1:4	

Table (2) shows the comparison between Graves' disease and thyroiditis concerning age, thyroid volume, and inferior thyroid arteries and depicts that the patients with thyrotoxicosis are younger than those with thyroiditis but the difference is a statistically non-significant. Thyroid volume in the thyrotoxicosis (22.14±7.56) is larger than the thyroiditis (11.92±4.68) in a statistically significant way. The systolic-diastolic ratio and resistive index are non-significantly different between the study groups.

Table (2): Shows the comparison between thyrotoxicosis and thyroiditis.

Study variables		Thyrotoxicosis	Thyroiditis	p-value*
Age (years)		35.5±3.54	38.3±6.24	0.057
Thyroid volume (cm^3)		22.14±7.56	11.92±4.68	0.001
Inferior Thyroid artery	R-PSV	62.81±19.30	21.45±11.63	0.001
	L-PSV	63.76±14.99	24.13±9.72	0.001
Inferior Thyroid artery	R-SD ratio	1.98±0.91	1.58±0.78	0.102
	L-SD ratio	2.05±0.65	1.69±0.76	0.078
RI		0.457±0.198	0.602±0.322	0.062
*t-test for independent two means				

Table (3) demonstrates the statistical characteristics of PSV, and shows that at the cut-off point of (61.50 cm/s); the sensitivity is 96.0%, while the specificity is 92.0%. Positive and negative predictive values are 92.3% and 95.8% respectively.

Table (3): Shows the statistical characteristics of PSV.

Indicator	Cut-off point	Sensitivity	Specificity	Positive predictive value	Negative predictive value
PSV	61.50	96.0%	92.0%	92.3%	95.8%

Table (4) and figure (1) demonstrate the area under the curve for the PSV and show that in the cut-off point of (61.50 cm/s), the AUC is (0.962) and is statistically significant at p=0.000.

Table (4): The area under the curve for the PSV.

Area	Std. Error[a]	p-value[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.962	0.032	0.000	0.898	1.000
The test result variable(s): PSV has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.				
a. Under the nonparametric assumption				
b. Null hypothesis: true area = 0.5				

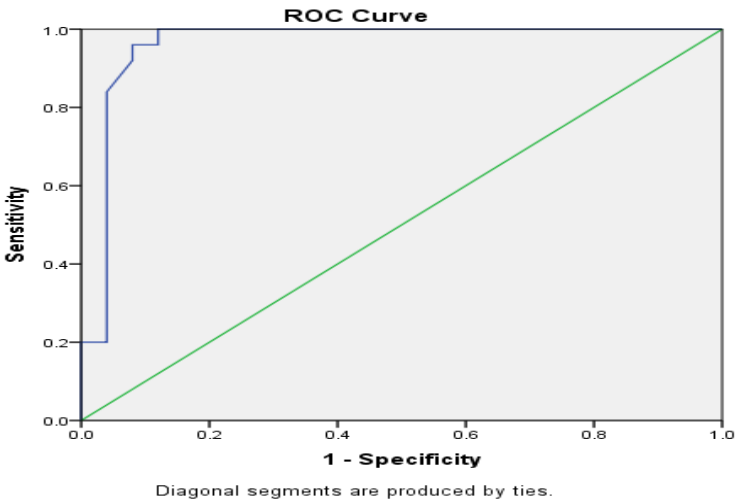


Figure (1): ROC curve for PSV.

DISCUSSION

The distinction between thyrotoxicosis and thyroiditis can be difficult, especially in cases of thyrotoxicosis that lack characteristic markers of the disease, such as ophthalmopathy or dermopathy, while the persistence of signs and symptoms can help distinguish thyrotoxicosis from thyroiditis. The condition must be diagnosed early in order to be properly managed.[37]

In the present study, 25 patients with thyrotoxicosis and 25 patients with Hashimoto's thyroiditis, the mean age for the sample was 36.9±4.89 years old, 20.0% were males and 80.0% were females.

The age of the patients in the present work had non-significant difference between thyrotoxicosis and Hashimoto's thyroiditis, although thyrotoxicosis in literature can occur at any age, but has a peak onset between 40 and 60 years.[38] Meanwhile, the thyroiditis may occur in teens or young women, it more often develops in women ages 30 to 50.[39]

Thyroid volume in normal subjects ranged from 5.6 ml to 20.2 ml, with a mean of 12.0 ± 4.0 ml. In patients with untreated thyrotoxicosis disease, the volume ranged from 13.3 to 190.7 ml with a mean of 40.2 ±27.8 ml[40], while large variations were noticed in thyroid volume have been reported in Hashimoto's thyroiditis[41], in the present study, the volume among thyrotoxicosis was significantly larger than that of thyroiditis which was similar to finding of a study done by Sundarram *et al*[42], the mean thyroid volume in thyrotoxicosis group was (28.9 ± 14.9) comparable to thyroiditis group patients (26.2 ± 8.81) (p = 1.324).

Peak systolic velocities of inferior thyroid artery in patients with thyrotoxicosis in current study, were significantly higher than patients with thyroiditis for both right (62.81±19.30) and left (63.76±14.99) inferior thyroid arteries. At the cut-off point of 61.50 cm/s, the sensitivity and specificity were 96.0% and 92.0% respectively in differentiation between thyrotoxicosis and thyroiditis.

A study done by Malik *et al.*,[44] showed that measurement of PSV-ITA by Doppler is a good diagnostic approach to discriminate between Thyrotoxicosis and thyroiditis with a sensitivity of 91% and specificity of 89% to differentiate between the two conditions but the cut-off level was 30 cm/s. Furthermore, Kurita and Cols[45], demonstrated in their study a sensitivity of 84% and specificity of 90% for CFDU in the differential diagnosis of thyrotoxicosis. And Donkol and Cols[37], in a study with 26 patients with thyrotoxicosis, demonstrated a sensitivity of 88.9% and specificity of 87.5% with doppler. 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.

Referring to the various studies[46-52], the present study found that the Doppler ultrasonography of the thyroid gland is considered to be one of the initial investigations that can give great help in the differentiation of thyrotoxicosis disease and Hashimoto's thyroiditis. Doppler is a cheap simple technique with no ionizing radiation exposure and is cost effective in the diagnosis of the thyrotoxicosis.[53-57]

End diastolic velocity is considered a Doppler parameter that reflects peripheral resistance.[58, 59] EDV is higher in thyroiditis patients than in individuals without thyroid disease.[60] This increase, in theory, reflects a reduction in the arterial blood flow resistance of the thyroid.[61] In the present study the systolic-diastolic ratio was assessed and found no significance between the study groups.

Although the resistive index in the current study found to be lower in thyrotoxicosis in comparison to the thyroiditis, statistically the difference was non-significant. Same result found in a study[62] done in

turkey, RI values in the thyroiditis group was 0.53±0.06 and 0.43±0.18 in the thyroiditis group (p<0.001).

CONCLUSION

Measurement of peak systolic velocity of inferior thyroid artery is a useful diagnostic tool for distinguishing between GD and thyroiditis, with high sensitivity and specificity.

Recommendations

1. Further studies should be conducted on larger size samples.
2. Using Doppler is a viable alternative to radioisotope scans in the diagnosis of thyrotoxicosis by measuring peak systolic velocity of inferior thyroid artery.

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