Ultrasonographic Assessment of the Thyroid Gland in Patients with Graves Disease Before and After Radioiodine Therapy - a Prospective Study

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Aims and objectives

Graves' disease (GD) is an autoimmune, diffuse, chronic pathology of the thyroid gland, first described by Robert Graves in 1835 [1]. It presents genetic predisposition and unknown etiology evidence, which is influenced in its development by several factors, including environment (dietary iodine intake, stress, drugs and infections). The disease is characterized by one or more changes: hyperthyroidism, goiter, ophthalmopathy, skin changes and pretibial myxedema, around 5% less common, and other symptoms 90 to 95%.

GD, the T lymphocytes become sensitive to antigens presented in thyroid gland, and stimulate B lymphocytes to synthesize antibodies against antigens. One of these antibodies, the TSH-R Ab is aimed against the TSH membrane receptor of thyroid cells and it is able to stimulate cells function. Circulating antibody is associated with disease positivity and recurrence.

This pathology incidence is higher in women (around 5 - 10:1) [2] [3], clearly in any age, although 20 - 40 years old more often. It is common in Caucasians and Asians, compared to blacks [4].

Pregnancy, excess iodine intake in certain regions, viral or bacterial infection, corticosteroids suspension, lithium treatment (alters immune system), are some factors that can stimulate immune response in GD.

Treatment options for hyperthyroidism caused by GD are: antithyroid drugs (tapazole, metimazol and propylthiouracil), radioiodine (131I) and, the last resort, surgery [3] [5]. The three treatments are effective, nevertheless, present problems and/or side effects, and none offers, an absolute cure for the disease.

One of the most relevant clinical practice, aspects in GD patients management is to distinguish GD in initial phase, from other types of destructive thyrotoxicosis, in addition to evaluate therapeutic methods and eficiente follow up, as well as predict early recurrence or remission of disease. Scintigraphy with pertechnetate (99mTc) and TSH levels dosage are considered the choice for this purpose. However, they present some technical difficulties, as they are not widely available and have contraindications [6] [7].

In this scenario, thyroid color-flow Doppler ultrasonography (US Doppler) presents a viable alternative, as a widely available, low cost, non-invasive and radiation free method, providing initial diagnosis and patients with GD follow up. In addition, this method is used in differential diagnosis with other causes of thyrotoxicosis in the early stage [6]-[10].

The aim of this study is to compare the ultrasonographic findings, Bmode and color-Doppler, in patients with Graves disease before and after radioiodine (131I) therapy.
3 and 6 months). To demonstrate the changes in the thyroid volume and parenchyma vascularization and in the systolic peak velocity of the inferior thyroid arteries after treatment.
Methods and materials

Fifty patients with Graves' disease were consecutively selected, of both gender, with no age distinction, with positive clinical and laboratorial findings of the disease and no prior radioiodine therapy.

This prospective study was conducted with IRB approval, after written informed consent be obtained from all participants.

An ultrasonography evaluation of the thyroid gland was performed before and after 131I therapy (1, 3 and 6 months).

The following aspects were evaluated: thyroid volume and parenchyma echogenicity, echotexture and vascularization. A systolic peak velocity for the inferior thyroid arteries was measured.

All examinations were performed by the same observer in the Department of Radiology, Clinics Hospital, University of São Paulo, SP, Brazil. The examinations were performed using the Philips IU 22 (Philips Ultrasound, Bothell WA, USA, 2009) and a linear transducer (5-12 MHz).

Statistical analysis

The statistical analysis was performed on MedCalc (Mariekerke, Belgium). A P value < 0.05 was considered significant.
Results

A progressive reduction in the average volume of the thyroid gland was observed from pre to post treatment evaluations, performed at 1, 3 and 6 months after radioiodo therapy (p < 0.05). The mean pre-treatment thyroid volume was 34.8 cm$^3$ and 1 month after treatment was 24.5 cm$^3$, showing a reduction of 29%. After the third month of treatment, the mean thyroid volume was 16.3 cm$^3$, representing a decrease of 34% compared to 1 month post treatment evaluation. After six months of treatment, the mean thyroid volume was 11.1 cm$^3$, representing a decrease of 68% from pre-treatment. All results were statistically significant (p < 0.05). Fig. 1 on page 6

The parenchyma echogenicity was subjectively evaluated. Before treatment, the thyroid gland parenchyma was markedly hypoechogenic and diffusely heterogeneous. During treatment there was an increase in the echogenicity of the parenchyma and a slight reduction its heterogeneity. Fig. 2 on page 6

The vascularization of the parenchyma in color Doppler scan was diffusely increased pre-treatment and declined progressively, but there was no returning to the usual standard of normality. Fig. 3 on page 6

We also analyzed the peak systolic velocity (PSV) in the lower thyroid arteries, right and left. The VPS inferior right thyroid artery had a mean pre-treatment of 80.69 cm/s and inferior left thyroid artery an average of 76.4 cm/s. One month after treatment the mean was reduced to 57.5 cm/s at right and 61.19 at left, respectively, showing a reduction of 29% and 20%. Fig. 4 on page 7 Fig. 5 on page 8

After the third month, the medium speeds decreased to 37.1 cm/s at right and 37.92 cm/s at left representing a reduction of 35% and 62%, respectively in relation to prior exam (1 month after the treatment). In the sixth month after the treatment, the VPS avarage in thyroid right artery was 34.17 cm/s and at left 32.89 cm/s, resulting in a sharper decrease than in previous months with medium reductions of 8 % at right and 15 % at left, in relation to prior exam (3rd month after treatment). In conclusion, the peak systolic velocities of thyroid arteries, right and left, showed decrease of 58%, at sixth month when compared to pre treatment velocities. All results were statistically significant (p < 0.5).
**Fig. 1:** Boxplot demonstrating the progressive decrease of thyroid dimensions volume since month 0 (pre treatment) and after 1, 3 and 6 months post treatment with radiodine (131I).

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**Fig. 2:** Changes in thyroid parenchyma characteristic of Graves’ disease are seen in B mode ultrasound. Reduced echogenicity and heterogeneous texture due to poorly delineated hypoechoic areas with fibrotic beams in between (A) After 6 months treatment with radioiodine, showing reduction in parenchyma volume (B).

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Fig. 3: Color Doppler scan of the right lobe in longitudinal section in a patient with Graves' disease without treatment, showing the sharp increase in vascularity of the parenchyma, the framework known as "thyroid inferno" (left image). The same patient after 6 months of treatment with radioiodine, showing reduction in vascularity of the parenchyma (right image).

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Fig. 4: Boxplot showing the progressive reduction in peak systolic velocity of right thyroid inferior artery from the month 0 (pre treatment) and after 1,3 and 6 months after treatment with radiodine (131I).
**Fig. 5:** Boxplot showing the progressive reduction in peak systolic velocity of left thyroid inferior artery from the month 0 (pre treatment) and after 1, 3 and 6 months after treatment with radiodine (131I).

**Fig. 6:** Spectral analysis of thyroid arteries systolic velocities (157 cm/s) markedly increased in patient with untreated Graves’ disease (A). The same patient after 6 months.
of treatment with radioiodine. There is normalization of systolic velocities (34.8 cm/s) in the Doppler spectrum thyroid arteries (B).

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Conclusion

Gland dimensions are usually enlarged, with global gland volume above normality, 6 to 15 cm³ [11]. In many cases, patients with GD are diagnosed and, consequently treated, when presenting large goiters, sometimes plunging, causing compression/deviation of adjacent structures such as trachea, esophagus and vascular structures, leading to dyspnea and dysphagia, and also, aesthetic discomfort to the patient.

Normal gland has an echogenicity characteristic in ultrasound, easily distinguishable from adjacent muscular structures. The thyroid gland ecogenicity is due to its follicular structure: the interface among thyroid cells and colloid produces high acoustic impedance, causing high frequency sound waves to be reflected back to the probe [12]. Resulting greater ecogenicity relative to the neck muscles and bigger or equal to the submandibular glands.

GD change the normal anatomic gland structure including diffuse heterogeneity and hypoechogenicity. In GD, hypoechogenicity is a result of hypervascularity and hypercellularity [13]. Vitti et al. [14] proved that in a study group including 105 patients, 70% of GD patients showed low thyroid gland echogenicity. This pattern is related to the TSH-receptor antibody (TRAb) higher positive frequency and hyperthyroidism recurrence.

In this study, we observed a statistical significant progressive reduction of thyroid volume after radioiodine therapy.

Color Doppler evaluation is GD ultrasonography diagnosis' next step, and probably the most important. Before GD treatment or effective therapy, there is a diffuse increase of the parenchyma vascularization, known as "thyroid inferno", a term first used to describe this phenomenon in Ralls et al. [15] publication, in 1988.

The thyroid gland vascularization correlates to the underlying functional status, decreases with the disease under control and can rise again in cases of recurrence. Many authors, observed that GD vascularity decrease occurred in parallel to the biochemistry remission and disease control, ratifying that thyroid US Doppler has the potential to monitor therapy response in patients with GD, as well as distinguish GD patients from Hashimoto thyroiditis, with similar B-mode pattern, without the use of expensive laboratory assays [6]-[10][15] [16] in their studies.

In spectral analysis, Macedo's study et al. [17], with US Doppler reference values in 84 healthy subjects without iodine deficiency, the normal SPV obtained was 24.80 cm/s and 25.85 cm/s in the superior thyroid arteries and 20.92 cm/s and 21.50 cm/s in the inferior thyroid arteries. The inferior thyroid arteries from the thyrocervical trunk while the superior ones comes from the external carotid arteries; for this reason is believed that the inferior thyroid arteries are less susceptible to hemodynamic changes.
Donkol et al. [8] considered the systolic peak velocity 40.0 cm/s in the inferior thyroid artery as higher and suggestive to GD, while most authors consider the velocity value above 50.0 cm/s for patients with this disease, values above 100.0 cm/s can be reached and not treated or not responsive to treatment [10] [18].

In our experience, a cut off 50.0 cm/s velocity is considered to GD diagnosis measurement in the inferior thyroid arteries, and we verify that patients responded to the treatment, presenting SPV reduction, while the parenchyma vascularity, although showing a significative reduction, remains increased when compared to the normal gland. In non-treated patients or non-responsive to the treatment no SPV decreasing is noted, so then US Doppler entitles is an excellent patient management method.

Thyroid arteries SPV method has become accurate and reliable, with excellent reproducibility [6] [7] [9] [18] in modern advanced technology.

Likewise, Varsamidis et al. (19) and Liu et al. (20) demonstrated decrease in peak systolic velocity (PSV) in patients with Graves disease after successful treatment. Before treatment, the VPS in the inferior thyroid artery averaged was 81.3 cm/s and after treatment were reduced to 28.9 cm/s. (19)

We observed a significant reduction of thyroid volume and velocity flow of the inferior thyroid arteries, demonstrating that ultrasound duplex-Doppler of the thyroid gland is an available and efficient method in the follow up of patients with Graves disease after radioiodine therapy.
References


