INVITED COMMENTARY

Grey scale thyroid ultrasonography in the evaluation of patients with Graves' disease

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Graves' disease is a genetically induced autoimmune disorder characterized by hyperthyroidism due to circulating thyroid stimulating hormone (TSH) receptor autoantibodies (TRAb) with thyroid stimulating activity (1). Graves' disease is the most common cause of hyperthyroidism, which has an estimated prevalence in iodine sufficient areas of 20/1000 females and 2.3/1000 males (2). It is most common in females between the ages of 20 and 50 years, but it may occur at any age. The laboratory diagnosis of Graves' disease is based on the finding of high serum thyroid hormone and undetectable serum TSH concentrations associated with circulating thyroglobulin and thyroperoxidase antibodies. TRAb is detectable in almost 90% of patients, but usually it is not needed for the diagnosis. Radioisotope scan of the thyroid shows a diffuse and homogeneous radionuclide uptake.

Treatment strategies for Graves' hyperthyroidism include medical therapy with antithyroid drugs (ATD) or thyroid ablation with ^{131}I or surgery. ATD, mainly thionamides, inhibit thyroid hormone synthesis by blocking iodine organification catalysed by thyroid peroxidase. Treatment of Graves' disease with thionamides is mainly performed in Europe and in Japan, while in the USA and Canada radioiodine is commonly preferred as the first choice treatment (3). Many studies have been undertaken to find parameters which help predict the clinical outcome of Graves' hyperthyroidism after ATD withdrawal. Among them, TRAb measurement at the end of an ATD course was found to be the most predictive (4, 5).

After its introduction into clinical practice in the late sixties, thyroid ultrasonography (US) proved to be very effective in the diagnostic approach to thyroid diseases, the anatomical location of the gland being advantageous for this technique. The most widely used application of thyroid US is identification and characterization of thyroid nodules (6). Rapid improvements in the development of US equipment have made available real-time high frequency transducers (7.5–10 MHz) with high resolution, which allow a more precise definition of the echostructure of the thyroid tissue. In addition, recently developed color Doppler technology allows determination of the blood flow through the gland, offering the possibility of recording objective measurements, such as the peak systolic

velocity of the blood flow at the level of thyroid arterial vessels (i.e. inferior thyroid artery). Using these techniques, thyroid blood flow has been shown to be correlated with the thyroid status in patients with Graves' disease, being markedly increased in 17/18 patients with untreated active hyperthyroidism and less clearly increased in treated patients. In patients with Hashimoto's thyroiditis, the thyroid blood flow was not correlated to thyroid status or treatment and was never markedly increased (7). Color Doppler sonography was also shown to be useful in distinguishing cases of destructive thyrotoxicosis by amiodarone (i.e. amiodarone thyrotoxicosis type 2), characterized by a low thyroid blood flow, from cases in which thyroid hyperfunction also occurs (i.e. amiodarone thyrotoxicosis type 1), characterized by an increased thyroid blood flow (8).

With grey scale US, the normal thyroid has a peculiar echo density, making the gland well distinguishable from surrounding neck muscles. Thyroid echogenicity is due to the gland's follicular structure: the interface between thyroid cell and colloid exhibits high acoustic impedance, causing high frequency acoustic waves to be reflected back to the probe. Conditions that change the normal anatomical structure of the gland cause this echo pattern to be altered.

Espinasse (1983) and Gutekunst *et al.* (1989) were the first to report abnormal thyroid ultrasound patterns, characterized by a diffuse low echogenicity, in patients with Hashimoto's thyroiditis and Graves' disease (9, 10). Marcocci *et al.* (11) found a diffuse low echogenicity in the thyroids of 44/238 patients with goiter and circulating thyroid autoantibodies. The degree of hypoechogenicity was significantly correlated with the levels of circulating thyroid autoantibodies. While thyroid function was normal in all 194 patients with normal thyroid echogenicity, hypothyroidism was found in 64% of those with thyroid hypoechogenicity. Histology of excised thyroid tissue from patients who underwent surgery for tracheal decompression showed diffuse lymphocytic infiltration in patients with thyroid hypoechogenicity, while in patients with normal thyroid echogenicity a histological pattern of colloid goiter with focal thyroiditis was found. These data clearly showed that thyroid hypoechogenicity was due to diffuse thyroiditis and

was correlated with hypothyroidism. In the same paper 59/90 (65%) patients with Graves' disease were found to have a diffusely low thyroid echogenicity. While diffuse lymphocytic infiltration accounts for thyroid hypoechogenicity in Hashimoto's thyroiditis, in Graves' disease the hypoechogenic pattern may be due to reduced colloid content with increased cellularity and reduction of the cell-colloid interface and/or to the increased blood flow (12).

Using ultrasonography, Vitti *et al.* (13) reported that about 70% of patients with Graves' disease exhibit a low thyroid echogenicity. Whatever the reason for thyroid hypoechogenicity in Graves' patients, this pattern is significantly associated with a higher frequency of TRAb positivity and with the relapse of hyperthyroidism. The study group included 105 patients who underwent a course of methimazole treatment. Thyroid ultrasonography was performed at diagnosis, and TRAb levels were measured at the end of treatment. During a 6–18 month follow-up period after methimazole treatment, 87/105 (83%) patients had relapse of hyperthyroidism and 18/105 (17%) were in remission. Recurrence of hyperthyroidism occurred in 71/76 (93%) patients with thyroid hypoechogenicity and in 16/29 (55%) of those with normal thyroid echogenicity. Positive TRAb values at the end of methimazole treatment were found in 59/76 (78%) patients with thyroid hypoechogenicity and in 12/29 (41%) patients with normal thyroid echogenicity. Sixty-five of eighty-seven (74%) patients with relapse of hyperthyroidism and 6/18 (33%) of those who remained euthyroid were TRAb-positive at the end of methimazole treatment. The finding of thyroid hypoechogenicity at diagnosis had higher specificity (0.81) and sensitivity (0.72) compared with TRAb positivity at the end of methimazole treatment (0.74 and 0.66, respectively) for the prediction of relapse of hyperthyroidism (13). Therefore, the evaluation of thyroid echographic pattern promised to be a useful prognostic tool in patients with Graves' disease.

Shieman *et al.* (14), studying 53 patients with Graves' disease, confirm that thyroid echogenicity is lower in these patients compared with that in 100 euthyroid volunteers. In agreement with the data of Vitti *et al.* (13), significantly lower echogenicity was found in patients with elevated TRAb levels and in those with active ophthalmopathy, suggesting that in some way this echographic pattern is associated with a more active disease. The merit of the paper of Shieman is the effort the authors made to obtain an objective measurement of thyroid echogenicity. To this purpose, the thyroid images obtained with a 7.5 MHz real-time transducer were recorded, keeping the operating conditions constant, and in selected regions of the thyroid the grey scale density was evaluated and translated into a numerical scale. The intra-assay and interassay variations of grey determination were <5%.

In the last few years, increasing evidence has been obtained indicating that thyroid US can be very useful in the diagnostic approach to thyroid autoimmune diseases, including Graves' disease. At present, thyroid US provides skilled operators with a useful method for diagnosing Graves' disease and for evaluating its severity. In the future, ultrasound imaging will prove increasingly useful as more sophisticated equipment is developed and operators increase their knowledge of color Doppler and three-dimensional technologies. Thus, ultrasound imaging is likely to increase in importance for diagnosis and follow-up of Graves' disease and become an essential technique for all thyroidologists.

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