CLINICAL STUDY

Standardized grey scale ultrasonography in Graves’ disease: correlation to autoimmune activity

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Abstract
Objective: Graves’ disease leads to thyroid enlargement and to reduction of tissue echogenicity. Our purpose was to correlate grey scale ultrasonography of the thyroid gland with clinical and laboratory findings in patients with Graves’ disease.
Design: Fifty-three patients with Graves’ disease were included in our study. 100 euthyroid volunteers served as control group. Free thyroxine (FT₄), TSH and TRAb (TSH receptor antibodies) values were measured and correlated with sonographic echogenicity of the thyroid gland.
Methods: All patients and control persons underwent ultrasonographical histogram analyses under standardized conditions. Mean densities of the thyroid tissues were determined in grey scales (GWE).
Results: Compared with controls with homogeneous thyroid lobes of normal size (25.6 ± 2.0 GWE, mean ± S.D.) echogenicity in patients with Graves’ disease was significantly lower (21.3 ± 3.3 GWE, mean ± S.D., P < 0.0001). Among the patients with Graves’ disease significant differences of thyroid echo levels were revealed for patients with suppressed (20.4 ± 3.1 GWE, mean ± S.D., n = 34) and normalized TSH values (22.5 ± 3.6 GWE, mean ± S.D., n = 19, P < 0.02). Significantly lower echogenicities were also measured in cases of persistent elevated TRAb levels (19.9 ± 2.9 GWE, mean ± S.D., n = 31) in comparison with normal TRAb levels (22.9 ± 3.5 GWE, mean ± S.D., n = 22, P < 0.0015). No correlation could be verified between echogenicity and either still elevated or already normalized FT₄ values or the thyroid volume. In coincidence of hyperthyroidism and Graves’ ophthalmopathy (19.7 ± 3.5 GWE, mean ± S.D., n = 23) significantly lower echogenicity was measured than in the absence of ophthalmological symptoms (22.3 ± 3.3 GWE, mean ± S.D., n = 30, P < 0.016). Patients needing active antithyroid drug treatment revealed significantly lower thyroid echogenicity (20.3 ± 3.1 GWE, mean ± S.D., n = 40) than patients in remission (23.7 ± 3.4 GWE, mean ± S.D., n = 13, P < 0.001). Statistical evaluation was carried out using Student’s t-test.
Conclusions: Standardized grey scale histogram analysis allows for supplementary judgements of thyroid function and degree of autoimmune activity in Graves’ disease. Whether these values help to estimate the risk of recurrence of hyperthyroidism after withdrawal of antithyroid medication should be evaluated in a prospective study.

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Introduction
Ultrasonography is an established method in the diagnosis of thyroid diseases (1–3). Apart from measurement of thyroid gland volume, ultrasonography is suitable to detect focal lesions like nodules or cysts. Moreover, ultrasonography contributes to the characterization of tissue echogenicity implying information about the follicular structure of the organ. Usually echogenicity of the thyroid gland is described as compared with the hyperechoic neck muscles (Mm. sternohyoidei, Mm. sternothyreoidei and Mm. sternocleidomastoidei), leading to definitions like hyper-, iso- or hypoechogenic thyroid tissue. This method includes, however, a major disadvantage: comparison of two different types of tissue is rather subjective. It depends on the visual impression and judgement of the investigator. In contrast, grey scale histograms of a well-defined region of interest represent an objective set of data reflecting underlying tissue echogenicity. In order to determine reproducible thyroid echo levels we defined constant sonographical operating conditions for survey of patients with Graves’ disease in correlation to their clinical and laboratory findings.

Patients and methods
Clinical and laboratory investigations
Fifty-three patients (44 females, 9 males, aged between 18 and 75 years) with Graves’ disease were included in
our study. The diagnosis of immunogenic hyperthyroidism was based on history or actual presence of common clinical criteria (tachycardia, weight loss, perspiration), diffuse hypoechogenic tissue pattern of the thyroid gland evaluated by ultrasound and laboratory parameters (elevated levels of circulating thyroid hormones (normal range for free thyroxine (FT₄) 10–23 pmol/l) or suppressed thyrotropin (TSH) values (normal range 0.35–4.5 mU/ml), determined radio-immunologically using commercially available kits (Chiron Chemiluminescence ACS 180) and elevated TSH receptor antibodies (TRAb assay, Henning, Berlin, Germany)). Results were expressed in U/l and values >10 were considered to be positive for the presence of TRAb. At time of exploration 40 patients had been receiving maintenance dosage of antithyroid drugs (5–20 mg methimazole) for 4–50 weeks and 13 patients had discontinued medication because of remission of the disease 5–20 weeks earlier. Graves’ ophthalmopathy was diagnosed according to the WHO classification. Patients were compared with 100 euthyroid volunteers (42 males, 58 females) with homogeneous thyroid lobe volumes (total volume <25 ml in males, <18 ml in females). They had never undergone thyroid lobectomy before and did not suffer from any other autoimmune disease.

Ultrasonographic investigations – grey scale histogram analysis

Thyroid ultrasonography was carried out by two of us (US, BR) using an ultrasound scanner (Picker CS 192, Espelkamp, Germany) with a 7.5 MHz linear real-time transducer. Patients were examined in the supine position, with the neck in hyperextension. The transducer was placed on the skin and longitudinal and transverse scans of the thyroid lobes were made. Focal lesions like nodules and cysts were excluded and vellumetry was performed according to Brunn et al. (4). Total volumes <25 ml for males and 18 ml for females were considered as normal. For the measurement of thyroid echogenicity we defined constant operating conditions. The following parameters were adjusted before each histogram analysis: ultrasound power level (high), brightness gain (30 dB), depth range (30–60 dB, graduated), frame rate (21/min), B-mode dynamic range, B-mode enhancement level and scan correlation. When starting up the measurement a histogram of up to 63 grey scales (GWE) within a specified region of interest (ROI) on a B-mode image was displayed. Photographs were recorded on Polaroid demonstrating the circumference (C), area (A), total number of grey scales (N), mean density, (MD), standard deviation (S.D.), density with highest frequency of occurrence (%Mode) and its frequency (%). For characterization of thyroid echo levels we defined the mean tissue density (MD) as relevant parameter which was determined in grey scales (GWE).

The interassay and intraassay variation of this ultrasonic method was <5% and the day-to-day variation was <3%.

Statistics

Statistical evaluation was carried out employing Student’s t-test. The level of significance was taken as P < 0.05. Data are given as confidence intervals of grey scales (GWE) in correlation with clinical or laboratory findings.

Results

Figure 1 shows transverse scans of the thyroid gland of a patient with euthyroid function, normal organ size and normal echogenicity under defined operating conditions. The MD of tissue echogenicity was measured with 24.4 GWE in the right and 25.6 GWE in the left thyroid lobe. In contrast, thyroid echogenicity of a patient with Graves’ disease (Fig. 2) was definitely lower (mean density of the right thyroid lobe 15.2 GWE and of the left thyroid lobe 15.7 GWE). Thyroid echo levels in 100 healthy volunteers who served as control group were between 21 and 32 GWE with an echogenicity of 25.6 ± 2.0 GWE, mean ± S.D.. Grey scales of patients with Graves’ disease were significantly lower with an echogenicity of 21.3 ± 3.3 GWE, mean ± S.D., n = 53, P < 0.0001 (Fig. 3). Thyroid echogenicity in patients with Graves’ disease and elevated FT₄ levels (20.8 ± 3.5 GWE, mean ± S.D., n = 36, P = 0.35). TSH suppression was correlated with significantly lower thyroid echogenicity (20.4 ± 3.1 GWE, mean ± S.D., n = 34) as compared with normalized TSH (22.5 ± 3.6 GWE, mean ± S.D., n = 19, P < 0.02).

In patients with persistently elevated TRAb levels grey scale histograms demonstrated significantly lower tissue echogenicity (19.9 ± 2.9 GWE, mean ± S.D., n = 31) as compared with patients with normalized TRAb levels (22.9 ± 3.5 GWE, mean ± S.D., n = 22, P < 0.0015). Echogenicity did not depend on the size of the thyroid gland. Patients with goitre (21.0 ± 4.1 GWE, mean ± S.D., n = 18) revealed the same echogenicity as patients with normal thyroid volume (21.2 ± 3.2 GWE, mean ± S.D., n = 35, P = 0.5). Graves’ disease coinciding with ophthalmopathy showed significantly lower thyroid echogenicity (19.7 ± 3.5 GWE, mean ± S.D., n = 23) than in the absence of ophthalmological symptoms (22.3 ± 3.3 GWE, mean ± S.D., n = 30, P < 0.016). Patients needing active antithyroid drug treatment revealed significantly lower echogenicity (20.3 ± 3.1 GWE, mean ± S.D., n = 40) than patients in remission (23.7 ± 3.4 GWE, n = 13, P < 0.001).
Ultrasonic tissue echogenicity of the thyroid gland depends on cellularity and vascularization of the organ. Reduced colloid content (5), lymphocytic infiltration (6) and increase of intrathyroidal flow (7) lead to hypoechoic tissue patterns. These characteristics are pre-described for Graves’ disease (8, 9) and Hashimoto’s thyroiditis (10, 11), suggesting that low thyroid echo levels are associated with or may predict the development of functional disorders like hyper- or hypothyroidism.

Normally, thyroid echogenicity is described as compared with the hyporeflective neck muscles. Zingrillo et al. tried to improve ultrasonographic classification of the thyroid gland defining an echogenicity score. The score included four categories: 0, absent; 1, mild; 2, moderate; and 3, marked hypoechoogenicity (9). The purpose of the present study was to specify thyroid echogenicity measurement in patients with Graves’ disease under standardized operating conditions with grey scale histogram analyses. This method which originally was developed for the differentiation between solid and cystic lesions (12, 13) and which was refined by other authors (14, 15) allows for quantitative determination of thyroid echo levels and is suitable for follow-up investigations.

As expected thyroid echogenicity in patients with Graves’ disease was significantly lower than in the control group. This is in accordance with other investigators (2, 16). Patients with TSH suppression or TRAb titre elevation showed significantly lower echo levels than those with normal values. Obviously persistent hyperthyroidism is associated with a higher grade of hypoechogenicity. Zingrillo et al. maintained that the grade of hypoechogenicity is a useful index for predicting recurrence (9). A normalized thyroid echo level in Graves’ disease may be more reliable in estimating the remission as laboratory measurements do (17) because it directly reflects morphological changes of the thyroid gland. Rubello et al. revealed that elevated TRAb levels and persistent hypoechogenicity of the thyroid gland were correlated with a high percentage

![Figure 1](https://example.com/image.png)
of recurrence of hyperthyroidism after withdrawal of medication (18). So far we suppose that withdrawal of antithyroid drug treatment will be more successful after normalization of tissue echogenicity. FT₄ values did not correlate to the hypoechogenic tissue pattern in Graves' disease as much as TSH. This could be due to the relatively prompt normalization of FT₄ levels in comparison with those of TSH levels under antithyroid treatment. The different kinetics of FT₄ and TSH in the correlation to the thyroid echogenicity emphasizes that the morphological appearance of the thyroid gland represents a long-term functional status.

**Figure 2** Transverse scan of the thyroid gland of a patient with Graves' disease under antithyroid drug treatment. The patient also suffered from Graves' ophthalmopathy. Grey scales (15.2 and 15.7 GWE) indicate significant hypoechogenicity.

**Figure 3** 95% confidence intervals for grey scales of patients with Graves' disease in comparison with control group patients. The difference was significant, with \( P < 0.0001 \) (Student's \( t \)-test).
Patients who suffered from autoimmune hyperthyroidism and Graves’ ophthalmopathy had more hypoechogenic tissue patterns than patients without ophthalmological symptoms. Indeed, this is an interesting result and in accordance with those of Becker and co-workers (2). At the moment there is no sufficient explanation for this phenomenon. We suppose that the grade of hypoechogenicity gives hints to the degree of autoimmune activity in Graves’ disease. This finding is in agreement with data from Vitti et al. who revealed that patients with highly elevated TRAb levels or coincidental ophthalmopathy have higher risks of recurrence of hyperthyroidism after antithyroid drug treatment (19, 20).

We conclude that standardized grey scale histogram analyses supply reproducible values of thyroid echogenicity and reflect the inflammatory status of the thyroid gland in patients with immunogenen hyperthyroidism. The ultrasonic hypoechogenicity is closely correlated with levels of TSH and TRAb. Patients in clinical and laboratory remission reveal significantly higher thyroid echogenicities than patients needing active antithyroid treatment.

Long-term studies have to be done, however, to verify if grey scale histogram analyses can help to predict the recurrence of hyperthyroidism after withdrawal of medication.

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References