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). 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 echogenities 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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our study. The diagnosis of immunogenic hyper-
thyroidism 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 labora-
tory parameters (elevated levels of circulating thyroid
hormones (normal range for free thyroxine (FT₄) 10–
23 pmol/l) or suppressed thyrotrophin (TSH) values
(normal range 0.35–4.5 μU/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’ ophthalmo-
pathy was diagnosed according to the WHO classifica-

tion.

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 = 17) was comparable to the

echogenicity in patients with Graves’ disease and
normalized FT₄ levels (20.7 ± 3.3 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 echo
levels 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 sig-
nificantly lower thyroid echogenicity (19.7 ± 3.5 GWE,
mean ± S.D., n = 23) than in the absence of ophthalmo-
logical 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 remis-

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.

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 transdu-
cer 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
volumetry 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 circum-
cumference (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%.
Discussion

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 hypoechogetic 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 hypoechogenicity (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 Transverse scan of the thyroid gland of a patient with euthyroid function and normal organ size. Grey scales (GWE) were measured in the ROI in both thyroid lobes. The thyroid echo levels are indicated as mean densities with 24.4 GWE in the right and 25.6 GWE in the left thyroid lobe.
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.
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 echo-genicity and reflect the inflammatory status of the thyroid gland in patients with immunogenie 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

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