Changes in thyroid volume during antithyroid drug therapy for Graves’ disease and its relationship to TSH receptor antibodies, TSH and thyroglobulin

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Abstract. Changes in thyroid volume during antithyroid drug therapy for Graves’ disease compared with circulating thyroid parameters were evaluated. One hundred and forty-four patients with Graves’ disease were treated with methimazole. Thyroid volume was measured by ultrasonography (thyroid volume = πabc/6, where a is length, b width, and c depth). Serum TSH, TSH-binding inhibitory immunoglobulins, thyroid-stimulating antibodies, thyroglobulin, antimicrosomal antibodies, and antithyroglobulin antibodies were also measured. In the whole group of patients, thyroid volume correlated significantly with thyroglobulin (p<0.01) and TSH-binding inhibitory immunoglobulins (p<0.01), but not with TSH, antimicrosomal antibodies, and antithyroglobulin antibodies. Furthermore, a positive correlation was found between thyroglobulin and TSH-binding inhibitory immunoglobulins (p<0.01). In 11 patients the mean thyroid volume decreased significantly after one year of therapy (p<0.01), associated with decreasing levels of serum TSH-binding inhibitory immunoglobulins. Ten patients experienced transient hypothyroidism with an overdose of methimazole, and the mean thyroid volume increased significantly (p<0.01) with increasing serum TSH levels. In conclusion, it is suggested that TSH receptor antibodies may have a thyroid growth-stimulating effect. In addition, circulating thyroglobulin levels reflect thyroid volume in Graves’ disease.

It is generally believed that the goitre decreases during antithyroid drug therapy in most patients with Graves’ disease. When an overdose of antithyroid drug is administered, the patient becomes hypothyroid and the goitre enlarges until reduction or withdrawal of the antithyroid drug. However, little information is available concerning such clinical concepts.

Recently, methods of estimating thyroid volume have been proposed by several investigators (1-3). Furthermore, several factors relating to goitre size, including TSH or thyroid stimulating immunoglobulins, have been suggested (4-8).

In the present study, we measured thyroid volume of patients with Graves’ disease during antithyroid drug therapy, and evaluated the relationships between thyroid volume and various thyroid parameters.

Patients and Methods

Studies were conducted in 144 patients with Graves’ disease (122 females, and 22 males, mean age 42 years, range 12-73 years). All patients were initially treated with 30 mg of methimazole. After normalization of serum free T₃ or free T₄ levels, the doses of methimazole were reduced.

Thyroid volume was determined by employing echocamera SSD-358 (Aloka, Tokyo), and was calculated according to the following formula described by Brown et al. (2):

Thyroid volume (ml) = (π/6)length×width×depth (cm)

In normal subjects (N=20, 17 females, and 3 males, mean age 34.5 years), the mean thyroid volume was 7.8±2.3 ml (mean±SD). Intra-assay variation was 4.0%.
Serum TSH was measured by immunoradiometric assay (IRMA). The minimal detectable limit of TSH was 0.03 mU/l. TSH-binding inhibitory immunoglobulins (TBII) were measured by radioreceptor assay (4,7). Thyroid stimulating antibodies (TS-ab) were measured by the method described by Kasagi et al. (5,6). Serum thyroglobulin (Tg) was also determined by radioimmunoassay in sera without antithyroglobulin antibodies. Free T4 and free T3 were measured by RIA. Antimicrosomal antibodies (Mi-ab) and antithyroglobulin antibodies (Tg-ab) were measured by passive hemagglutination.

Statistical analysis was performed using Student’s t-test and paired t-test. The level of significance was chosen at 0.05.

Results

In the whole group of patients studied, thyroid volume correlated significantly with Tg (p<0.01, Fig. 1) and TBII (p<0.01, Fig. 2), but not with TSH, TS-ab (Fig. 3), Mi-ab and Tg-ab. No significant difference in the mean thyroid volume was found among various titres of Mi-ab (Fig. 4). On the other hand, a positive correlation was found between Tg and TBII (p<0.01, Fig. 5).

Eleven patients were followed during one year of treatment with the antithyroid drug. After one year of therapy, the mean thyroid volume had decreased significantly (p<0.01, Fig. 6). The mean serum TBII level had decreased significantly (p<0.01, Fig. 6).

Ten patients experienced transient hypothyroidism with overdoses of the antithyroid drug. The mean thyroid volume increased significantly with increasing serum TSH (p<0.01, Fig. 7). After normalization of the thyroid function by reduction or withdrawal of methimazole, the mean thyroid volume decreased significantly (p<0.01, Fig. 7).

Discussion

Brown & Spencer (2) estimated thyroid volume, using a standard geometric formula: volume of an ovoid = \( \pi \times \frac{a}{6} \times b \times c \) (a: height, b: width, c: thickness). The length, width and depth of the thyroid lobes were measured from ultrasonic scans in addition to scintigraphy. This simple approach to estimation of
thyroid volume was justified by the good correlation between the estimated volume and surgical findings ($r=0.92$). We applied Brown’s method to estimating thyroid volume because of simplicity and sufficiency.

There have been several reports on the relationship between thyroid stimulators and thyroid volume. Hegedüs et al. (9) and Bliddal et al. (10) found a positive correlation between thyroid volume and TBII or TS-ab before treatment as well as during treatment. In our studies on 144 patients with Graves’ disease, thyroid volume correlated with TBII (Fig. 2), but not with TS-ab (Fig. 3). It is possible that our assay system of TS-ab was more sensitive than that of other investigators. Further

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**Fig. 4.**
The mean thyroid volumes among various titres of antimitosomal antibodies (MCHA) in Graves’ disease (not significant).

**Fig. 6.**
Changes in thyroid volume and serum thyroid-binding inhibitory immunoglobulins (TBII) during methimazole treatment in patients with Graves’ disease (*$p<0.01$ vs time 0).

**Fig. 5.**
Correlation between serum thyroid-binding inhibitory immunoglobulins (TBII) and serum thyroglobulin in Graves’ disease ($N=79$, $r=0.38$, $p<0.01$).

**Fig. 7.**
Changes in thyroid volume and serum TSH in transient hypothyroidism owing to overdoses of methimazole (*$p<0.01$ vs hypothyroidism).
studies are needed to elucidate the differential sensitivity of the two assay systems, TS-ab and TBII.

Berghout et al. (11) described that in healthy adults no relations were found between thyroid volume and parameters such as TSH, T3, T4 and Tg. In diffuse non-toxic goitre, Feldt-Rasmussen et al. (12) found a positive correlation between thyroid volume and serum Tg. We have demonstrated a positive correlation between thyroid volume and serum Tg in patients with Graves’ disease (Fig. 1). In addition, serum Tg correlated significantly with serum TBII (Fig. 5). Patients with hyperthyroidism owing to Graves’ disease usually have enlarged thyroid glands, associated with elevated serum thyroid hormone concentrations, and abnormal thyroid immunoglobulins, such as TSH receptor antibodies. It has been clearly demonstrated by several investigators that either TSH receptor antibodies or TSH will stimulate the release of Tg from thyroid cells (13-16).

Recently, it has been proposed that thyroid growth-stimulating immunoglobulins contribute to goitre formation in human thyroid autoimmune disease (17-19). Drexhage et al. (16) reported that thyroid growth-stimulating immunoglobulins correlated well with goitre size in untreated Graves’ disease. It has been suggested recently that thyroid growth-stimulating immunoglobulins and TS-ab are identical in Graves’ disease (10,20).

The present study demonstrated that most of the patients with Graves’ disease obtained a reduction of goitre size during antithyroid drug therapy, associated with decreasing serum TBII levels (Fig. 6). Apparently, the enlarged goitre of untreated patients with Graves’ disease is somewhat related to TSH receptor antibodies. It was also demonstrated that in transient hypothyroidism owing to overdoses of methimazole, the goitre grew with increasing serum TS-ab levels (Fig. 7), suggesting that increasing levels of TSH had a thyroid growth-stimulating effect.

In conclusion, the thyroid volume decreased during methimazole treatment with decreasing serum TBII levels. In contrast, in patients with transient hypothyroidism owing to the overdoses of methimazole, the thyroid volume increased with high levels of serum TSH. Further studies are needed to reevaluate changes in thyroid volume before and after antithyroid drug therapy in a longitudinal design with a sufficiently large population. It is also of interest to investigate whether such changes in thyroid volume are related to relapse of Graves’ disease. The data obtained herein suggest that TSH and TSH receptor antibodies may have a thyroid growth-stimulating effect, and Tg reflects thyroid volume in patients with Graves’ disease during therapy.

References

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