A Quantitative Analysis of Orbital Soft Tissue in Graves' Disease Based on B-mode Ultrasonography

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Synopsis

Using B-mode ultrasonography, an attempt was made to measure the volume of extraocular muscles and retrobulbar fat in 31 patients (62 orbits) with Graves' disease. None of the patients had exophthalmometric measurements greater than 21 mm or had eye symptoms. The mean value of muscle volume of Graves' patients was significantly larger than that of normal controls (6.48±2.70 cm³ and 3.25±1.30 cm³, respectively, p< 0.001). All of the patients had extraocular muscle swelling, although 2 of them had no extraocular muscle change for their unilateral eye. The extraocular muscle volume increased as the degree of the proptosis increased. The fat volume tended to increase in parallel with the degree of the proptosis. In the Graves' group with obvious proptosis (Hertel reading: 19-21 mm), the fat volume increased more significantly than in any other group. The ratio of extraocular muscle volume to retrobulbar fat volume was significantly higher in Graves' disease, but it did not increase as the degree of the proptosis increased. A significant correlation between proptosis and muscle volume plus fat volume was observed. No significant difference of the extraocular muscle volume was observed between the patients untreated and treated with antithyroid drugs. The data show a uniform enlargement of the extraocular muscles in Graves' disease and also suggest an involvement of increased retrobulbar fat volume in a group of obvious exophthalmos. The degree of the proptosis is in close proportion to the quantitative change of the orbital soft tissue.

B-mode ultrasonography had been shown to be a sensitive method for detecting orbital involvement in Graves' disease (Coleman et al., 1972b; Werner et al., 1974; Forrester et al., 1977). Previous papers reported a frequent occurrence of ocular muscle swelling in ultrasound detection of Graves' disease (Werner et al., 1974; Forrester et al., 1977). In these reports, the ocular protrusion was not necessarily parallel to the degree of muscle swelling, based on semiquantitative analysis. On the other hand, several papers showed pathological changes of retrobulbar fat tissue in Graves' exophthalmos (Rundle and Pochin, 1944; Riley, 1972; Smelser, 1937). In this connection, we attempted a quantitative analysis of acoustical image of orbital soft tissue to determine a possible involvement of retrobulbar fat together with extraocular muscle swelling in Graves' disease. The correlation between proptosis and changes in orbital soft tissue was also analyzed.

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Materials and Methods

Thirty one patients of Graves' disease were studied for their bilateral orbits. Seventeen were untreated and 14 treated with antithyroid drugs but not in remission. Six euthyroid diabetic patients with negative thyroid autoantibody test were assessed as controls. A diagnosis of Graves' disease was established on the basis of clinical and laboratory findings (serum T4, serum T3, 24h 131I uptake, T3 suppression test, and thyroid autoantibodies to thyroglobulin and microsomes). All patients investigated in this study were included in class 0 according to the modified classification of the eye changes of Graves' disease by the American Thyroid Association (Werner, 1977).

Equipments and Technique

B-mode ultrasonography of high resolution was performed as described elsewhere with some modifications (Coleman et al., 1972a). Equipments for the ultrasonographic diagnostic set were Aloka-SSD-60B and a scanner for ophthalmology with transducer of 5 megahertz (diameter: 13 mm, focus: 55 mm). Serial scans of the orbit were made, and the oscilloscopic image was monitored and recorded in the videotape. After the scan was performed, the recorded tape was displayed and photographed to provide a permanent scan record. Horizontal scans were made that permitted the examination of the lateral and medial walls of orbit and the orbital apex. A caution was paid to scan at the position where the maximal diameter of bilateral eyeballs and lateral rectus muscle were obtained. It was indispensable for analytical evaluation to get clear echo of medial orbital wall which was hard to depict clearly because of its sagittal position.

Estimation of the volume of extraocular muscles and retrobulbar fat

Tracing maps of the oscilloscopic image was depicted on the paper and the figure was made as follows (Fig. 1). A line ("line a") tangent to the lateral orbital wall (L) is drawn. Then a line ("line b") tangent to the medial orbital wall (M) is drawn to make the inclination angle of both lines 45°. The intersecting point (A) is assumed to be the deepest point of the orbital apex. An eyeball is figured as a circle of 24 mm in diameter, bouding on the acoustical image of retrobulbar fat tissue. From the center of the circle (C), the perpendicular lines to "line b" and "line a" are drawn and the crossing points are designated as B and D respectively. The perpendicular line on the middle point (E) of distance A-D is drawn and its crossing point on the surface of the area representing retrobulbar fat tissue (area indicated as fat) is designated as G. The distance E-G is measured in mm and the value represents "muscle index". The area of the extraocular muscles (shaded area indicated as Muscle) and the retrobulbar fat are measured with planimeter. The volume is calculated by the formula: $V = S \times \sqrt{S}$ (V: volume, S: area). The value of 24 mm for the diameter of eyeball is dependent on the mean value for Japanese adults (Shoji, 1966) and 45° for the angle of orbital apex on the data of computerized tomography of the orbit. The volume of optic nerve is not calculated on the assumption that it does not share the bulk change of Graves' disease. The statistical data shown in this text represent mean±S.D. and the statistical significancy is analyzed by Student's t test.

Results

The extraocular muscles and orbital wall were sharply represented in the control group which enabled us to calculate the volume of extraocular muscles and retrobulbar fat.
fat (Fig. 2). The extraocular muscles of Graves' patients also appeared clear but the space between retrobulbar fat and orbital walls was increased, indicating the enlargement of the muscles. The volume of the orbit was calculated with the formula as mentioned in Materials and Methods. The orbital volume of the control group was 25.4 cm$^3$ which closely accorded with the data of measured Japanese orbital volume (24.0–26.7 cm$^3$) (Shozi, 1966). To assess the degree of proptosis in Graves' disease and controls, 113 patients of Graves' disease and 140 euthyroid patient of diabetes mellitus were examined for their proptosis with Hertel type exophthalmometer. Proptosis in Graves' disease was significantly increased beyond normal by about 3 mm (17.09 ± 2.79 mm and 14.10 ± 2.64 mm, respectively, p < 0.001) (Fig. 3). The samples assessed for the acoustical change were also distributed in the same range (Graves' disease: 16.59 ± 3.26 mm, controls: 14.45 ± 0.83 mm, p < 0.05). Comparing the muscle volume and the "muscle index" of Graves' disease with those of controls, both value increased significantly in Graves' disease (Table 1). The samples were divided into 4 groups according to the degree of proptosis measured with Hertel type exoph-
thalmometer (Table 2). The Graves' patient without proptosis (group II) showed a significant increment of the muscle volume as compared with controls (group I), though both groups had the same extent of the Hertel readings. The muscle volume increased as the degree of the proptosis increased in Graves' patient, although group II did not differ from group III (I: 3.25±1.35 cm³, II: 5.65±2.57 cm³, III: 5.65±1.84 cm³, IV: 8.94±2.44 cm³) (Fig. 4). The same pattern was observed in the “muscle index” (I: 3.07±1.30, II: 4.62±2.29, III: 6.34±1.68, IV: 7.72±3.42).

The muscle volume and the “muscle index” were correlated closely, indicating that the “muscle index” was a simple and easy indicator of the muscle volume (r=0.797, p<0.001). The ratio of the muscle volume to the fat volume (Vm/Vf ratio) was also compared between both groups. The value was obviously smaller in controls than in any group of Graves' patients (p<0.001). There was no significant difference between 3 groups of Graves' patients (I: 0.69±0.28, II: 1.19±0.40, III: 1.11±0.37, IV: 1.29±0.51) (Fig. 5). The fat volume in groups I, II and III did not differ significantly.

Fig. 4. Changes in the extraocular muscle volume in Graves' disease. The extraocular muscle volume was calculated as mentioned in Materials and Methods. The groups I-IV were divided as indicated in Table 2.

Fig. 5. Changes in the Vm/Vf ratio in Graves' disease. The volume of extraocular muscles and retrobulbar fat was calculated as mentioned in Materials and Methods. The groups I-IV were divided as indicated in Table 2.
from one another but it tended to increase as the degree of proptosis increased. Group IV increased fat volume than any other group significantly (Table 3). The correlation between proptosis and the muscle plus fat volume was analyzed and shown to have a close relation (Fig. 6). The statistically significant correlation was also observed between proptosis and the muscle volume \( Y = 0.53X - 3.60, \ r = 0.663, \ p < 0.001 \). No correlation was observed between the muscle volume and laboratory data of thyroid function (serum T4, serum T3, thyroid autoantibodies to thyroglobulin and microsomes, IgG, IgM and IgA) (data not shown). The muscle volume and the \( V_m/V_f \) ratio were compared between the group of untreated patients and that of treated patients. Both value of patients on antithyroid drugs were similar to those found in untreated patients (Table 4).

**Discussion**

High resolution ultrasonography of the orbital soft tissue has been performed in Graves' disease and the quantitative evaluation of the volume of extraocular muscles and retrobulbar fat is attempted. The validity of the assumed formula for calculation of volume is proved by the coincidence of the calculated orbital volume in the control group and the mean value for measured orbital volume of Japanese. In this study, the patients without any eye symptoms were evaluated in order to confirm a frequent incidence of orbital change in Graves' disease. All patients of Graves' disease studied show an enlargement of the orbital muscle. Only 2 orbits out of 62 (3.23\%) have a similar volume of their extraocular muscle to those of controls. In a large random sample of Graves' disase, the ocular protrusion was found to be increased beyond normal by about 3 mm. It is possible that in most patients in whom no exoph-
thalmos is diagnosed clinically, ocular pro-
trusion of less than 3 mm has already been
found, though not in their healthy state. Rundle (1964) reported that in wasted
subjects the orbital tissue decreased in bulk
and the eye became sunken, while in obese
subjects the orbital contents were bulky and
the eyeball was more prominent than in
normal subjects. It is likely that in Graves’
disease the bulk change of the orbital tissue
compensates for the recession of the eye
which is caused by wasting. Our data
also suggest a possible role of the orbital
fat tissue leading to eye protrusion. Rundle
and Pochin (1944) have reported the in-
creased orbital fat volume together with
enlarged extraocular muscles in autopsies
that the fatty replacement observed by
Rundle and Pochin (1944) might have fol-
lowed the subsidence of the inflammatory
phases. Biopsies of the orbital fat tissue
from patients with Graves’ disease have
shown the focal accumulation of inflam-
matory cells: lymphocytes (Riley, 1972;
Smelser, 1937). The changes are variable
to a great extent between the specimens from
different patients. The same changes are
also observed by electronmicroscopy (Riley,
1972). There is an increased quantity of
stainable mucopolysaccharide in the inter-
stitial space (Wegelius et al., 1957).

In this study, the retrobulbar fat volume
increased as the proptosis developed. The
fact that the Vm/Vf ratio does not change
while muscle volume increases indicates
that both extraocular muscles and retro-
bulbar fat swellings are in parallel as exophthal-
mos progresses. Presumably in severer cases,
the orbital fat change is an element of
the protrusion. The fatty changes we ob-
served may not be of burned out of muscle
swelling which was suggested by Werner
(1974) because the patients we studied had no
symptoms of extraocular muscle involvement.
The proptosis was in close mutual relation
with the volume of the muscle or muscle
plus fat. The gradient of the regression
line differs between two parameters (muscle
volume alone: 0.53, muscle plus fat vol-
ume: 1.11). An experimental study on the
mechanics of exophthalmos was reported
by injecting molten paraffin wax into the
human retrobulbar space post mortem
(Rundle and Wilson, 1944). They plotted
protrusion against the increase in orbital
volume. The gradient of the line was 1.02.
The value is in accord with the gradient
of the protrusion-volume relationship of
muscle plus fat volume.

In conclusion, it is suggested that the
increased orbital fat volume is an element
of the ocular protrusion. The proptosis is
in close proportion to the quantitative
change of the orbital tissue. Even the
smallest increase in the bulk of the orbital
tissue may cause some protrusion. In di-
agnosis and following the progress of exo-
phthalmos, a quantitative analysis of the
orbital soft tissue based on B-mode ultra-
sonography is quite useful. For the routine
survey of the extraocular muscle change
in Graves’ disease, calculation of “muscle
index” is convenient because of its ease.
Calculation of the Vm/Vf ratio is recom-
ended for detecting the minimal changes
of the orbital tissues.

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