Volumetric measurements in Graves’ orbitopathy
Regensburg, N.I.

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Do subtypes of Graves’ Orbitopathy exist?

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Abstract

PURPOSE To describe the prevalence of fat and muscle volume increase in Graves’ orbitopathy (GO) patients, calculated from computed tomography (CT) scans, and the associated ophthalmic and endocrine characteristics.

DESIGN Consecutive observational case series.

METHODS Volumetry using age-specific reference values in untreated GO patients who had been rendered euthyroid.

PARTICIPANTS 95 consecutive Caucasian GO patients attending the thyroid-eye clinic.

MAIN OUTCOME MEASURES subgroups in GO and main characteristics.

RESULTS Four subgroups could be distinguished: group 1, no fat volume (FV) or muscle volume (MV) increase (N=24), group 2, only FV increase (N=5), group 3, only MV increase (N=58) and group 4, both FV and MV increase (N=8). Patients with an increase of MV were older and had higher TBII, more proptosis and more impaired ductions than those without MV increase. Patients with an increase of FV differed from those without FV increase only in having more proptosis. The clinical activity score did not differ between the four groups.

CONCLUSIONS 25% of GO patients have orbital fat and muscle volumes within age-specific reference range. An increase of the fat volume is seen in only 14% of GO patients and characterized by proptosis. Muscle enlargement occurs in 70% of patients and is associated with older age, higher TBII values, more proptosis and impaired motility.
Introduction

Graves’ disease is a multisystem auto-immune disorder affecting the thyroid gland, the orbits, the pretibial skin and the acra of the fingers. Orbital involvement or Graves’ orbitopathy (GO) consists of a variable combination of eyelid retraction and eyelid swelling, proptosis, impaired motility and occasionally of optic nerve compression. Orbital volumetric changes explain most of these symptoms. Hufnagel et al. showed the huge enlargement of the extraocular muscles that can be found in GO patients.1 Rundle et al. mentioned de novo adipogenesis in GO.2 The transition of a subset of (activated) orbital fibroblasts into adipocytes, is now regarded to be a key event in the pathogenesis of GO.3-5 The introduction of computed tomography (CT) scanning and magnetic resonance imaging (MRI) made clear that, patients with GO show a spectrum of orbital soft tissue volume changes, ranging from pure muscle volume (MV) to pure fat volume (FV) increase, as can be appreciated from the pictures shown in figure 1.

Figure 1, computed tomography scans of 2 patients with Graves’orbitopathy. One with only increase in fat volume (left), the other with only increased muscle volume (right).

In line with these findings is the observation by Nunery et al. that some GO patients mainly show proptosis and/or lid retraction, whereas others mainly have motility impairment.6,7 Zonneveld hypothesized that orbits in GO can be categorized in four groups: group 1, no increase of FV or of MV; group 2, only FV increase; group 3, only MV increase; and group 4, both FV and MV increase.7 If such groups do exist, they might have different characteristics and may need a different therapeutic approach.

Up till now it has been difficult to test this hypothesis, because no accurate and validated tools for the calculation of orbital soft tissue volumes existed, nor were there any reference values at our disposal. However, this has changed since we introduced such a tool and, at least for Caucasians, assessed the age-related reference values.8,9 So in this study, our aim was to calculate FV and MV in GO patients, to see if we can group them according to increased FV and/or MV and to assess specific ophthalmic and endocrine characteristics.
Patients and methods

Between June 2005 and June 2008, we studied consecutive patients with presumed GO, referred to the Department of Ophthalmology of the Academic Medical Centre of the University of Amsterdam, the Netherlands. Patients were referred to our combined thyroid-eye clinic. In a single day the patients visited the laboratory, the endocrinologist, the orthoptist and the ophthalmologist. A CT scan was made and if necessary a visual field. At the end of the day the patients were evaluated by consultants in ophthalmology and endocrinology in a combined session to reach a final diagnosis. The patients were classified according to the NOSPECS classification (No signs and symptoms, Only signs, Soft tissue involvement, Proptosis, Extraocular muscle involvement, Corneal involvement and Sight loss) and the Clinical Activity Score (CAS).

Patients were included if they were older than 20 years of age (to exclude changes due to ongoing growth), Caucasian (to exclude racial differences in orbital volumes as described by for instance by Barretto, Furuta, Fledelius), and were diagnosed with definite GO by the attending consultants in ophthalmology and endocrinology. Patients were excluded, if they refused to participate, had biochemical overt hypo-or hyperthyroidism (high FT4, in combination with abnormal TSH), were pregnant, were known drug abusers, had received previous treatment for their orbitopathy other than lubricants (radiotherapy / immunosuppressive treatment or surgery), had an incomplete set of CT images or an uncorrected Gantry-tilt on CT. Out of the 143 consecutive referrals, 95 patients met our inclusion and exclusion criteria. The tenets of the declaration of Helsinki were followed. Although our Ethical Committee considered this study not subject to consent, all participants were asked to sign an informed consent.

From the CT-scans the soft tissue volumes were calculated using the software “Mimics®”, as described previously. By using the ratios of fat-volume/orbital-volume (FV/OV) and muscle-volume/orbital-volume (MV/OV), anatomical differences between men and women were eliminated as described by Regensburg et al. The ratios of the 190 orbits were compared with reference values. All MV/OV- and FV/OV-ratios above the 97.5 percentile (P) of controls (e.g., age specific cut-off values) were used for categorization. Then, of each patient, the orbit with the largest MV/OV-ratio was chosen. If the MV/OV-ratio of both orbits did not differ, we chose the orbit with the largest FV/OV-ratio. If there was neither a difference of the MV/OV-ratio, nor of the FV/OV-ratio, we chose the orbit to be evaluated at random. Finally, we divided the patients into 4 groups: group 1, no increase in FV or in MV; group 2 (all values below the 97.5 percentile); group 2, only FV increase (FV/OV-ratio > P 97.5); group 3, only MV increase (MV/OV-ratio > P 97.5); and group 4, FV and MV increase (both ratios > P 97.5).

The following clinical parameters were evaluated, age, gender, FV/OV-ratio, MV/OV-ratio, Best Corrected Visual Acuity (BCVA), color vision, lid swelling and lid aperture, upper and lower scleral show, lagophthalmus, exophthalmometry with a Hertel exophthalmometer, diplopia-score according to Gorman, abduction, adduction, elevation, depression,
and the Clinical Activity Score (CAS). Laboratory measurements included TSH (Thyroid Stimulating Hormone), FT4 (Free Thyroxin), TPO-ab (Thyroid Per Oxidase antibodies), and TBII (TSH Binding Inhibitory Immunoglobulin).

Exophthalmometry was performed by 2 ophthalmologists independently from each other. The patient was sitting in upright position looking at a fixed spot at 4 meters distance. Both eyes were measured simultaneously with the same Hertel-exophthalmometer (Oculus). In the rare case of discrepancy, the third measurement of the most experienced consultant was decisive. Lid aperture was measured with a ruler in millimeters, the patient sitting relaxed in upright position and fixating a spot at 4 meters...

Statistical analysis was performed using “SPSS 16.0.2.” T-test for equality of means was used for differentiation between GO patients and controls. Where appropriate, the non-parametric tests of Kruskal-Wallis and of Mann-Whitney U tests were used. A p-value less than 0.05 was considered to be statistically significant.

Results

Out of 143 consecutive referrals, 48 patients had exclusion criteria: 13 were non-Caucasian, 10 had biochemically overt hyperthyroidism, 9 had been treated with oral Prednisone, 1 had undergone decompression surgery, 10 stacks of images were incomplete and 5 patients had no GO. Of the 95 included GO patients were 86 female.

Scatter plots, showing the values of the FV/OV- and MV/OV- ratios of our patients, are given in figure 2 in relation to their age.

The percentiles P=2.5 and P=97.5 of control orbital soft tissue volumes are shown in the plots for comparison. Both the MV/OV- and the FV/OV- ratios differed significantly from controls (p=0.000 and p=0.03 respectively).

24 orbits showed no increase of fat or muscle volume (group 1), 5 orbits only showed FV increase (group 2), 58 orbits only MV increase (group 3) and 8 orbits both FV and MV increase.

Figure 2, scatter plots of the ratios fat volume/ orbital cavity volume (FV/OV) and muscle volume/orbital cavity volume (MV/OV) versus age (years). Lines indicate the P2.5 and P97.5 of age-specific reference values.

1 Oculus Optik Geraete, Wetzlar, Germany
Figure 3. 3D (dimensional) reconstructions of the fat volume and extra ocular muscle volume in four Graves’orbitopathy patients representative for group 1 (no increased fat or muscle volume), group 2 (only increased fat volume), group 3 (only increased muscle volume) and group 4 (increased fat- and muscle volume).
Do subtypes of Graves’ Orbitopathy exist?

Table 1, Characteristics of Graves’orbitopathy patients according to volumetric measurements, figures are median values with interquartile range between brackets;

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (N=24)</th>
<th>Group 2 (N= 5)</th>
<th>Group 3 (N=58)</th>
<th>Group 4 (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FV and MV &lt;97.5</td>
<td>Only FV&gt;97.5</td>
<td>Only MV&gt;97.5</td>
<td>FV and MV&gt;97.5</td>
</tr>
<tr>
<td>FV/OV</td>
<td>0.56 [0.50-0.63]</td>
<td>0.75 [0.67-0.79]</td>
<td>0.57 [0.50-0.65]</td>
<td>0.83 [0.80-0.93]</td>
</tr>
<tr>
<td>MV/OV</td>
<td>0.16 [0.15-0.17]</td>
<td>0.17 [0.14-0.19]</td>
<td>0.24 [0.21-0.28]</td>
<td>0.25 [0.22-0.33]</td>
</tr>
<tr>
<td>Diplopia score*</td>
<td>0 [0-0]</td>
<td>0 [0-0]</td>
<td>1 [0-2]</td>
<td>0 [0-1]</td>
</tr>
<tr>
<td>TSH (mu/L)</td>
<td>1.6 [0.0-7.5]</td>
<td>0.6 [0.0-2.5]</td>
<td>0.64 [0.1-3.0]</td>
<td>1.5 [0.6-4.2]</td>
</tr>
<tr>
<td>TBIi (U/L)</td>
<td>4.4 [1.9-9.2]</td>
<td>2.7 [1.0-3.9]</td>
<td>9.9 [2.8-22.6]</td>
<td>5.5 [0.5-22.1]</td>
</tr>
</tbody>
</table>

group 1(no increase in fat- or muscle volume= both <97.5), group 2 (only increase in fat volume), group 3 (only increase in muscle volume) and group 4 (increase in fat- and muscle volume= both >97.5). FV/OV= orbital fat volume/bony orbital cavity volume. MV/OV= extraocular muscle volume/bony orbital cavity volume. ^proptosis measured with Hertel exophthalmometer. *0=no diplopia, 1=intermittent diplopia, 2= inconstant diplopia correctable with prisms, 3= constant diplopia. # degree. CAS= clinical activity score. TSH= thyroid stimulating hormone. FT4= free thyroxin. Anti TPO= thyroid per oxidase antibodies. TBII= thyroid binding Inhibitory immunoglobulins. Kruskal-Wallis test. p<0.05 is considered significant.

As an illustration, figure 3 shows three dimensional reconstructions of the fat body and of the extra ocular muscle volume in patients from these four groups. Some investigated parameters with the p-values of differences between the groups are summarized in table 1.

The Kruskal-Wallis test demonstrated, that the four groups differed significantly in the following parameters: age (p=0.02), FV/OV (p=<0.00), MV/OV (p=<0.00), proptosis (Hertel values, p=0.00), diplopia score (p=0.00), ductions (p=0.01 and twice 0.03) and TBIi (p=0.02). All other parameters (treatment with I131 ,length, weight, BCVA, color vision, lid swelling, upper scleral show, lower scleral show, lagophthalmus, depression, CAS, TSH, FT4, T3, anti-TPO) did not differ significantly.

Comparing the groups with and without MV increase (group 1 and 2 versus group 3 and 4) (Table 2), we found that patients with increased MV were older (age p=0.00), had more proptosis (Hertel values, p=0.02), more impaired ductions (abduction (p=0.00) adduction (p=0.00) and elevation (p=0.01)), more diplopia (score p=0.00) and higher TBIi (p=0.01). Relative to patients without an increased FV (groups 1 and 3), patients with increased FV (groups 2 and 4) had more proptosis (Hertel values, p=0.00) and less diplopia (score p=0.05).
This study shows that, by calculating the orbital fat and EOM volumes, GO-patients can be divided into four groups: with no FV or MV increase, with only FV increase, with only MV increase and with both FV and MV increase.

Twenty-four out of 95 patients (25%) appeared to have no FV or MV increase. This justifies the question whether these patients were correctly diagnosed. Maybe, they had no GO after all? However, the diagnosis GO had been made by experienced endocrinologists and orbitologists during a thyroid-eye clinic. Incidentally, patients referred to the combined thyroid-eye clinic were found to have no Graves’ orbitopathy. In fact, in 5% of all referrals no diagnosis of GO could be made. All GO patients, although rendered euthyroid, had a history of Graves’ hyperthyroidism and had the clinical presentation of proptosis and/or eyelid retraction, for which no other cause than GO could be found. In addition, photographs (figure 4) of these patients were used for a secondary evaluation and all patients were again diagnosed with GO.

### Table 2

Differences in characteristics of Graves'orbitopathy patient groups, in relation to increased fat- and/or muscle volume. Figures are median values with interquartile range between brackets.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>FV/OV &gt;97.5</th>
<th>FV/OV&lt;97.5</th>
<th>p=</th>
<th>MV/OV &gt;97.5</th>
<th>MV/OV&lt;97.5</th>
<th>p=</th>
</tr>
</thead>
<tbody>
<tr>
<td>2+4</td>
<td>13</td>
<td>48 [42-54]</td>
<td>50 [43-58]</td>
<td>0.43</td>
<td>52 [47-59]</td>
<td>45 [36-51]</td>
<td>0.00</td>
</tr>
<tr>
<td>1+3</td>
<td>82</td>
<td>0.81 [0.73-0.86]</td>
<td>0.57 [0.50-0.65]</td>
<td>0.00</td>
<td>0.59 [0.53-0.69]</td>
<td>0.6 [0.5-0.67]</td>
<td>0.58</td>
</tr>
<tr>
<td>3+4</td>
<td>66</td>
<td>0.22 [0.18-0.26]</td>
<td>0.21 [0.18-0.26]</td>
<td>0.97</td>
<td>0.24 [0.21-0.28]</td>
<td>0.16 [0.15-0.17]</td>
<td>0.00</td>
</tr>
<tr>
<td>proptosis(mm)^</td>
<td>24</td>
<td>21 [19-23]</td>
<td>0.00</td>
<td>22 [21-24]</td>
<td>20 [19-23]</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>diplopia score*</td>
<td>0</td>
<td>1</td>
<td>0.05</td>
<td>0</td>
<td>0</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>abduction</td>
<td>46</td>
<td>46 [40-50]</td>
<td>0.74</td>
<td>45</td>
<td>40-48</td>
<td>48</td>
<td>45-55</td>
</tr>
<tr>
<td>adduction</td>
<td>46</td>
<td>46 [43-49]</td>
<td>0.83</td>
<td>45</td>
<td>40-48</td>
<td>48</td>
<td>45-51</td>
</tr>
<tr>
<td>elevation</td>
<td>43</td>
<td>40 [30-47]</td>
<td>0.84</td>
<td>40</td>
<td>26-46</td>
<td>45</td>
<td>34-52</td>
</tr>
<tr>
<td>CAS</td>
<td>2</td>
<td>2</td>
<td>0.82</td>
<td>2</td>
<td>1-3</td>
<td>2</td>
<td>1-3</td>
</tr>
<tr>
<td>TSH(mu/L)</td>
<td>0.76</td>
<td>1</td>
<td>0.96</td>
<td>0.82</td>
<td>0.1-3.3</td>
<td>1.1</td>
<td>0.0-5.3</td>
</tr>
<tr>
<td>FT4 (pmol/L)</td>
<td>17</td>
<td>15.2</td>
<td>15.5</td>
<td>0.07</td>
<td>15.5</td>
<td>12.1-17.9</td>
<td>14.9</td>
</tr>
<tr>
<td>AntiTPO (kU/L)</td>
<td>240</td>
<td>140</td>
<td>0.41</td>
<td>1.2</td>
<td>15-620</td>
<td>160</td>
<td>40-3000</td>
</tr>
<tr>
<td>TBII (U/L)</td>
<td>3</td>
<td>7.4</td>
<td>9.7</td>
<td>0.10</td>
<td>2.6-22.6</td>
<td>4.2</td>
<td>1.9-8.2</td>
</tr>
</tbody>
</table>

**Footnotes:**
- *group 2+4 = with fat volume increase, group 1+3= without fat volume increase. group 3+4= with muscle volume increase, group 1+2= without muscle volume increase. FV/OV= orbital fat volume/orbital bony cavity volume. MV/OV= extraocular muscle volume/orbital bony cavity volume. \(^{\text{\textsuperscript{\textdegree}}}^{\text{\textsuperscript{\textdegree}}\text{proptosis measured with Hertel exophthalmometer. 0=no diplopia, 1=intermittent diplopia, 2=inconstant diplopia, 3= constant diplopia. Ductions expressed in degrees. CAS= clinical activity score. TSH=thyroid stimulating hormone. FT4= free thyroxin. Anti TPO= thyroid per oxidase antibodies. TBII= thyroid binding inhibitory immunoglobulin. Kruskal-Wallis test. p<0.05 is considered significant.**

**Discussion**

This study shows that, by calculating the orbital fat and EOM volumes, GO-patients can be divided into four groups: with no FV or MV increase, with only FV increase, with only MV increase and with both FV and MV increase.

Twenty-four out of 95 patients (25%) appeared to have no FV or MV increase. This justifies the question whether these patients were correctly diagnosed. Maybe, they had no GO after all? However, the diagnosis GO had been made by experienced endocrinologists and orbitologists during a thyroid-eye clinic. Incidentally, patients referred to the combined thyroid-eye clinic were found to have no Graves’ orbitopathy. In fact, in 5% of all referrals no diagnosis of GO could be made. All GO patients, although rendered euthyroid, had a history of Graves’ hyperthyroidism and had the clinical presentation of proptosis and/or eyelid retraction, for which no other cause than GO could be found. In addition, photographs (figure 4) of these patients were used for a secondary evaluation and all patients were again diagnosed with GO.
Moreover, GO in the absence of extraocular muscle swelling has previously been reported.\textsuperscript{17} Finally, the median Hertel value in group 1 is above the average Hertel value in Caucasians.\textsuperscript{14} So we conclude, that GO can exist in the absence of FV or MV increase on CT or MRI scans.

The explanation for (mild) proptosis and/or lid retraction in combination with an absence of FV and MV increase can only be speculative. It is not impossible, that the FV was actually increased relative to the pre-diseased state, but this increase did not exceed the 97.5 percentile of controls and was therefore not shown in our analysis.

It is interesting to speculate that the patients without fat and/or muscle volume increase were at the beginning of their orbitopathy course. Support, however, for this assumption could not be given by our data. Their CAS did not differ from other groups, as could be expected in GO patient with a recent onset of disease. It would be interesting to follow this group to see whether increase of FV or MV will take place in the future.

Being a tertiary referral centre may have led to bias in our final subgroup description. Patients with early disease, and therefore possibly less muscle and fat volume increase, are referred nowadays more often than in the past. Patients with DON (Dysthyroid Optic Neuropathy), and possibly only muscle volume increase, are usually referred urgently and immediately treated and thus did not participate in our thyroid-eye clinic.

We observed an increase of FV in group 2 (without MV increase) and in group 4 (with MV increase) compared to the reference values, accounting for 14\% of the investigated patients. To the orbitologist performing orbital decompression surgery, this percentage may seem low. However, up till now, the prevalence of fat increase has been based on clinical impressions and not so much on measurements. The radiological diagnosis of fat increase on a CT- or MRI-scan was based on the position of the globe and the swelling of the extraocular muscles. The presence of proptosis in combination with slender muscles then was considered to be the result of fat increase.\textsuperscript{17} We found FV increase to be related to more proptosis and less diplopia, but not with any other ophthalmic or endocrine parameter.

We found an increase of fat- and muscle volume in only 8\% of our patients. In contrast to Forbes, who observed an increase of FV and MV in 46\% of his patients.\textsuperscript{18} But neither Forbes’ calculations nor his normal values were corrected for age or race.
MV increase was present in by far the largest group. Seventy percent of our patients had MV increase. MV increase was found to be related to older age, higher TBII titers, more proptosis and, as could be expected, reduced duction values. We previously reported that the MV decreases with age in control subjects (Regensburg et al. 9); hence the correlation of MV increase with older age and higher TBII values raises some questions. First, does the MV increase take place in a later stage of the disease? The absence of difference in CAS values between groups in our study, do not support such a hypothesis. Second, is perhaps the manifestation of GO age-dependent? There is evidence that the course of GO is worse in elderly people. 19 Eckstein (2006) however found no correlation of increased TBII with age, but higher TBII was correlated with the severity of the disease. 20 Third, the association with higher levels of TBII in the MV increase groups may indicate, that these antibodies play a role in the pathogenesis of GO. Research as to the exact interaction of TBII with the EOM is however difficult to undertake, since there is no reliable animal model.

Based on volumetric calculations, four subgroups of GO can be distinguished and that these groups show ophthalmologic and endocrine differences. These findings may shed a different light on the diagnosis and treatment of GO patients and raises intriguing questions regarding the pathogenesis of GO.
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References