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Natural Course of Mild Graves Orbitopathy: Increase of Orbital Fat But Decrease of Muscle Volume With Increased Muscle Fatty Degeneration During a 4-Year Follow-Up

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Purpose: To describe the natural course of orbital fat volume and extraocular muscle volume in mild Graves orbitopathy during a 4-year follow-up. To describe fatty changes within the extraocular muscles.

Patients: Twenty-five patients with mild Graves orbitopathy, who did not require any therapeutic intervention other than supportive therapy, were followed for 4 years.

Methods: CT scans were performed in all patients at baseline and follow-up. A validated technique using Mimics (Materialise) was used to calculate fat and muscle volumes. Outcomes were compared with previously collected data. The amount of intramuscular fat was assessed on CT scans in a semi-quantitative way by two blinded observers according to a four-point scale.

Results: After a median follow-up of 4.3 years, the median fat to orbital volume ratio increased with 0.08 from 0.57 to 0.65 ($p = 0.000$), whereas the median muscle volume to orbital volume ratio decreased with 0.03 from 0.17 to 0.14 ($p = 0.000$). In this control group in patients between 49 and 54 years old, the changes were 0.01 and −0.002, respectively. The Clinical Activity Score decreased to zero ($p = 0.000$), and the median eyelid aperture decreased from 12 to 10 mm ($p = 0.007$). A significant increase of intramuscular fat was found in patients with Graves orbitopathy.

Conclusions: The natural course of mild Graves orbitopathy, as observed over 4 years, is characterized by an increase of orbital fat volume, a decrease in muscle volume, and an increased intramuscular fatty degeneration.

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Graves orbitopathy (GO) is an autoimmune disease characterized by eyelid retraction, proptosis, and motility impairment.[1] GO is closely related to Graves hyperthyroidism and Graves dermopathy (pretibial myxedema).[2] About 60% of patients have only mild complaints and symptoms (irritation, watering eyes, eye lid swelling, and upper eyelid retraction), whereas 30% has significant symptoms interfering with daily life activities (disfiguring proptosis, diplopia) and 5–10% develop corneal involvement or optic nerve compression.[3]

Rundle[4], in the middle of the last century, studied the natural course of GO and demonstrated that the symptoms of GO in the early phase of the disease increase in severity, then reach a plateau phase and finally decrease again, although do not necessarily get back to normal. To a certain extent, GO can therefore be considered a self-limiting disease. In the initial phase by Rundle[4], the eyelids are red and swollen, and patients experience pressure feeling or pain behind the globes and on attempted up-, side-, or downgaze. The authors call this the active phase of the disease in contrast to the later or quiescent phase, in which pain, swelling, and redness have disappeared, but proptosis and diplopia may still be present. At present, the treatment strategy is based both on the severity and the activity of GO.[5]

The authors studied the natural course of (mild) GO in terms of volume changes. To calculate the orbital soft tissue volumes, the authors used a fixed and validated method.[6] In a previous article, the authors presented their results after 1-year follow-up.[7] The authors showed that muscle volume (MV) increase is an early phenomenon, and fat volume (FV) increase is a relatively late phenomenon in the course of GO. The present study is a continuation of this previous study with a much longer follow-up of 4 years. The aims are as follows: 1) How do orbital muscle and FVs in patients with mild and untreated GO develop in the long run and how are these changes related to the course of clinical parameters, and 2) Is fatty degeneration within the extraocular muscles part of the natural course of GO?

PATIENTS AND METHODS

This study was approved by the Medical Ethics Committee of the Academic Medical Center of the University of Amsterdam, the Netherlands. The tenets of the declaration of Helsinki were followed.

Between January 1, 2004, and the December 31, 2011, in the Academic Medical Center in Amsterdam, the authors studied 25 patients with mild GO who did not require specific eye treatment and only received artificial tears. These patients were part of a larger group of 95 untreated GO patients referred to the Academic Medical Center between 2004 and 2011, in whom volumetric measurements had been performed by Regensburg et al.[8] Patients had been included if they were older than 20 years of age and were diagnosed with definite GO by the attending consultants in ophthalmology and endocrinology in a combined thyroid eye clinic. They had not received any specific treatment (radiotherapy/immunosuppressive treatment or surgery) for their orbitopathy other than lubricants during the observation period. Patients were clinically and biochemically euthyroid during the entire study period. Seventy patients of the original group were excluded in the present study because over the years they had had some kind of treatment interfering

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with the inclusion criteria or because they did not want to participate anymore in this follow-up study. Soft tissue volumes were calculated from CT scans, obtained in the course of routine clinical evaluation on first visit, second visit (after 1 year), and third visit (after 3–5 years). To minimize bias by racial differences in orbital anatomy, non-Caucasian were excluded. All participants gave signed informed consent before participating in this study, and the tenets of the declaration of Helsinki were followed. Disease severity and activity were classified using the **N**o signs and symptoms, **O**nly signs, **S**oft tissue involvement, **P**roptosis, **E**xtraocular muscle involvement, **C**orneal involvement and **S**ight loss classification system[9] and the Clinical Activity Score.[10] Measurements were taken by a single observer. Ophthalmic measurements include visual acuity, Hertel values, diplopia, lid aperture, upper and lower limbal to lid margin distance, pupillary reactions, ocular movement, lagopthalmos, and color vision. For double vision, the authors used the Gorman score for diplopia; for example, grade 0: no diplopia; grade 1: intermittent (only when tired or on awakening); grade 2: inconstant (only at extremes of gaze); grade 3: constant (in primary gaze or reading position).

(Change of) smoking habits were registered. OU/ both orbits were used for calculation of volumes and analysis. Follow-up period ranged from 3 to 5 years.

Outcomes were compared with previously collected data,[11] in which the authors constructed regression lines of FV to orbital volume ratio (FV/OV) and MV to orbital volume ratio (MV/OV) as a function of age in healthy individuals. Linear regression analysis in this study, with the ratios FV/MV and MV/OV as dependent variables and both age and sex as independent variables, showed a significant correlation for FV/OV and age, but this correlation was independent of gender. MV/OV showed a significant, negative correlation with age in women. Thus, in healthy women, the FV/OV and MV/OV for each age can be calculated using the formula FV/OV = 0.00337 × age + 0.3902 and for MV/OV = 0.00027 × age + 0.1602.[11] (Fig. 2) For women at the age of 53, the FV/OV thus appears to be 0.57 and at the age of 49 years, 0.56. So over 4 years, the authors assess an increase of FV/OV of 0.01 in healthy female controls. Similarly, the MV/OV rises in these controls between 49 and 53 of age with 0.002 from 0.173 to 0.175.

Computational Volumetric Assessment. The CT scans were acquired in the axial plane and uploaded in a workstation. The Mimics 17 software (Materialise NV, Researchpark Haasrode, Louvain, Belgium) was used to get multiplanar reconstructions into coronal and sagittal images. Orbital FV and MV could then be calculated in cubic millimeters (mm^3). Orbital FV and MV of the four extra ocular muscles (EOM) were selected on the masks with region growing (computer-assisted separation of different tissues) and manual segmentation and differentiation using the software Mimics following the protocol described previously by their group.[6] The FV/OV and MV/OV were used to eliminate anatomical differences between genders.[11] The median and interquartile range was used for the ratios, because they were not normally distributed.

Semi-Quantitative Assessment of Fatty Changes Within the EOM. CT scans were judged to assess the total amount of fatty degeneration of the ocular muscles (EOM) of OU at baseline and after a 4-years of follow-up. Assessment was done at a random order by a blinded ophthalmologist specialized in orbital surgery and a blinded radiologist specialized in head and neck radiology, including ophthalmology and orbitology. Scans were graded from 0 to 3; 0 for no fatty degeneration of the muscles, 1 for mild, 2 for moderate, and 3 for marked fatty degeneration.

Statistical Analysis. Statistical analysis was performed using SPSS for Mac version 21.0 (SPSS Inch, Chicago, IL). The Wilcoxon test was used for differences within one group, and the Mann-Whitney U test for differences between two unrelated groups. A p value of < 0.05 was considered statistically significant.

RESULTS

The median follow-up of the 25 patients with mild and untreated GO (22 women and three men) was 4.3 years. Orbital CT scans were performed at baseline and after 3–5 years. In 15 of these 25 patients, CT scans were also made after 1 year of follow-up. Three patients were smoking at baseline; two of them stopped during follow-up.

The FV/OV ratio slowly increased from 0.57 (0.50–0.65) at baseline to 0.65 (0.57–0.69) after 4 years, whereas the MV/OV ratio decreased from 0.17 (0.16–0.20) at baseline to 0.14 (0.12–0.15) in 4 years, in particular between the last two visits. More characteristics of this group of GO patients are given in Table.

Figure 1A,B shows individual changes in FV/OV and MV/OV ratios. All patients but two had an increase in FV/OV during the follow-up period, and all patients had a decrease in MV/OV after 4 years. After 1 year, half of patients had an increase in MV/OV and the other half had a decrease in MV/OV; the median MV/OV of the whole group remained stable. Figure 2 shows the median and interquartile range of FV/OV and MV/OV of all patients depicted against the follow-up visits. The FV/OV mostly increased in the year following diagnosis, and the MV/OV remained stable during the first year and decreases thereafter.

At the baseline visit, there was little to no fatty degeneration of the EOMs (score of 0 (interquartile range [0–1]). At the last visit, some fattening of the extraocular muscles was noted on the scan {score of 1 (interquartile range [1–2]), $p = 0.000$} (Fig. 3). No correlation was found between measured MVs and the grade of muscle fattening.

DISCUSSION

It will come as no surprise that little is known about the natural course of GO. For obvious reasons, the natural course can only be studied in patients who do not need interventional treatment.[12] Therefore, a limitation of this study is that their conclusions in this article only refer to GO patients with mild and not to those with moderately severe or severe GO.

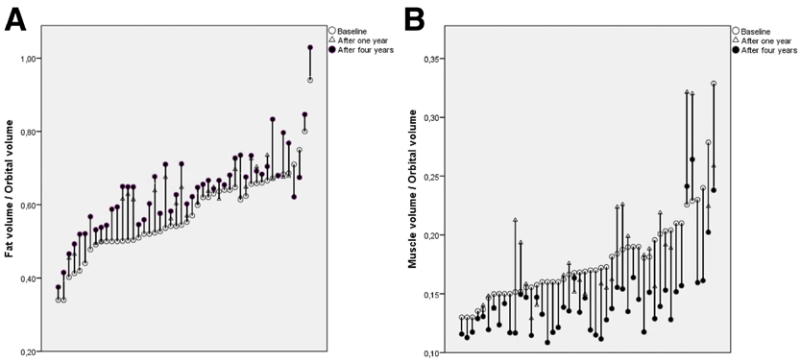

FIG. 1. Orbital soft tissue changes. **A**, Changes of the orbital fat volumes over 4 years in 25 patients with mild Graves orbitopathy (GO). **B**, Changes of the orbital muscle volumes over 4 years in 25 patients with mild GO.

Natural Course of Eye Changes in Patients With Mild Graves Orbitopathy Followed for 4 Years

Clinical and Orbital Soft Tissue Parameters	Baseline (n = 25), Median (Interquartile Range)	After 1 Year (n = 15), Median (Interquartile Range)	After 4 Years (n = 25), Median (Interquartile Range)	*p*
Age (years)	48.8 (43.7–62.7)	50.45 (44.91–64.18)	53.57 (47.05–59.22)	0.000
Fat volume (ml)	15.01 (12.84–16.64)	15.52 (14.34–17.43)	16.84 (14.24–18.73)	0.000
Muscle volume (ml)	4.50 (4.21–7.72)	4.28 (3.76–5.33)	3.52 (3.17–3.88)	0.000
FV/OV	0.57 (0.50–0.65)	0.62 (0.57–0.67)	0.65 (0.57–0.69)	0.000
MV/OV	0.17 (0.16–0.20)	0.17 (0.15–0.21)	0.14 (0.12–0.15)	0.000
Lid aperture (mm)	12 (10–13)	12 (11–14)	10 (9–11)	0.007
Hertel value (mm)	20 (17–22)	20 (18–22)	19 (18–21)	0.584
Diplopia*	0 (0–0.7)	0 (0–1)	0 (0–0)	0.628
CAS	1 (1–2)	1 (0–1)	0 (0–1)	0.000

*Gorman score; see text.
CAS, Clinical Activity Score; FV/OV, fat to orbital volume ratio; MV/OV, muscle volume to orbital volume ratio.

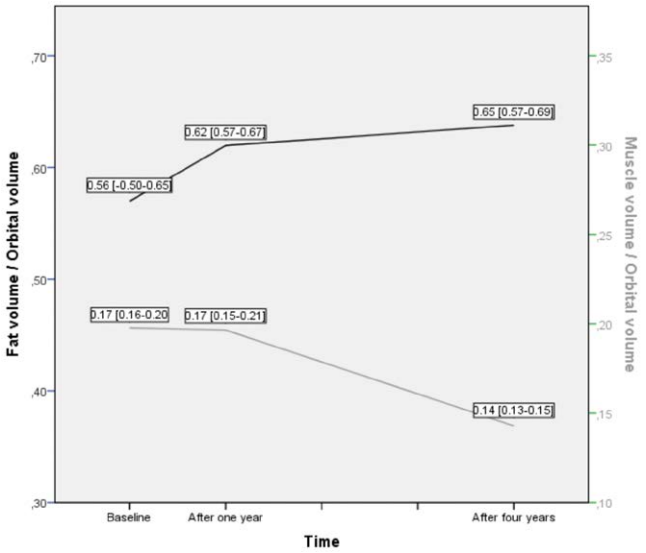

FIG. 2. Orbital fat and muscle volumes in patients with mild Graves orbitopathy (GO) depicted against time. Numbers are median, between bracket: interquartile range (IQR) 25–IQR75.

Hales and Rundle[13] were the first to assess that GO is a self-limiting disease, although they realized that not all symptoms disappear completely. In a series of 346 patients with newly diagnosed and recent onset Graves hyperthyroidism, Tanda et al.[14] demonstrated that more than 80% of patients without GO at baseline did not develop GO after an 18-month follow-up period, whereas patients with mild GO had spontaneous remission in 50% of cases. This finding is in accordance with the study of Perros et al.[15] who studied the natural course of GO in 59 untreated patients and found that 13 patients (22%) improved substantially, 25 patients (42.4%) showed minor improvement, 13 patients (22%) did not change, and eight patients (13.5%) deteriorated progressively to the extent that immunosuppressive treatment was considered to be necessary.

Their volumetric studies are in line with clinical studies: the MV decreases as does the Clinical Activity Score and the lid aperture. However, and this is a novel finding, the authors also assessed an increase of orbital fat that comes when the Clinical Activity Score tapers down. The authors calculated a mean increase of 1.83 ml of orbital fat and a decrease of 0.98 ml in MV over 4 years. One might suggest that the volumetric changes found can be explained by aging. However, comparing the FV/OV and MV/OV changes in this study (e.g., 0.08 and −0.03, Table) with changes in age-matched (49–53) healthy women in their control group (e.g., 0.01 and 0.002),[11] it becomes obvious that aging alone cannot explain the changes. Another confounding factor might be the smoking habits of the included patients. The significance of smoking in GO is striking.[16] In their previous study, however, the increase of orbital fat after 1 year was observed both in 12 current smokers, as in 27 ex-smokers and never smokers.[7] In the present study, there were only three smokers of whom two stopped immediately after their first consultation.

In another previous article, the authors demonstrated in a group of 95 untreated GO patients, that at their first consultation, 70% of all patients had an increase in MV, while 14% had an increase of FV.[17] MV increase seems thus the most prominent feature at the beginning of the disease and decreases after the first year. The increase in orbital fat is a rather late phenomenon, it mainly occurs in the first year of the disease, and after the first year the increase tapers down. Proptosis did not reduce significantly in their studies. Proptosis in GO is notorious for its immutability. In fact, the recent experience with teprotumumab by Smith et al.[18] is one of the first in which substantial reduction of proptosis has been described. It would be the most interesting to calculate the orbital soft tissues following the application of

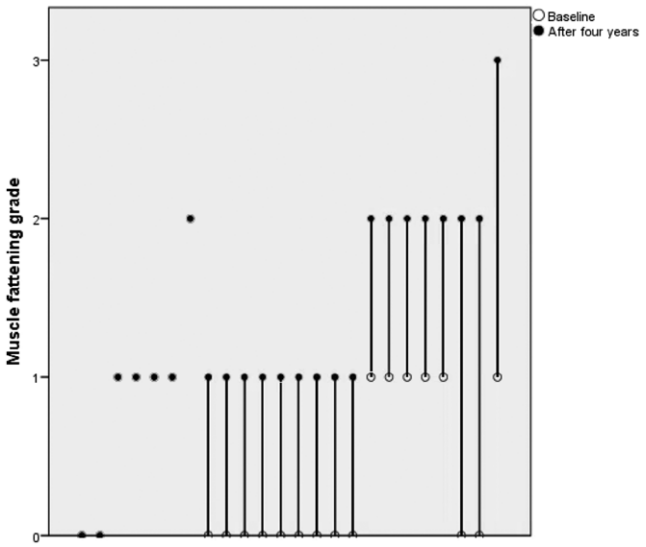

FIG. 3. Changes of intramuscular fatty degeneration in 25 patients with mild, untreated Graves orbitopathy (GO) after 4 years, arranged accordingly (1) amount of change, (2) initial volume.

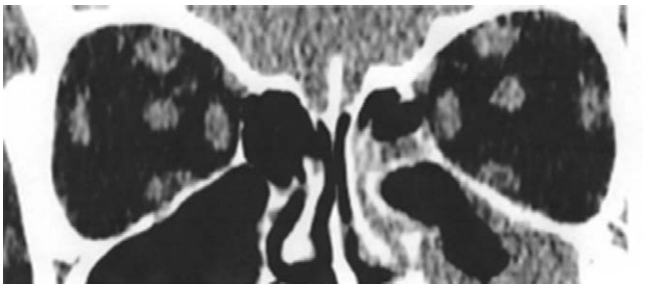

FIG. 4. Coronal CT scan showing fatty degenerations within extraocular muscles (dark areas within lighter areas).

teprotumumab and see what changes are responsible for this proptosis reduction. Perhaps teprotumumab not only influences the inflammatory changes of the extraocular muscles but also prevents the second stage of GO, neoadipogenesis?

The presence of intramuscular fat together with intramuscular edema and fibrosis in the extraocular muscles of GO patients has been described already in 1972 by Riley et al.[19] and is quoted in successive papers usually without any comments.[20] More interest in fatty degeneration of (skeletal) muscles is to be found in the endocrine and orthopedic literature. Hamrick et al.[21] argue that "fibro/adipogenic progenitors or mesenchymal interstitial cells are present in normal muscle tissue and readily differentiate into adipocytes under various conditions such as muscle injury or glucocorticoid treatment". McKelvie et al.,[22] in a postmortem study in 1999, examined the age-related changes in extraocular muscles in healthy individuals and assessed age-dependent changes of variation in muscle fiber size, increased endomysial fibrous tissue, and increased endomysial adipose tissue. These changes begin to become common after the age of 60 years. Kirkland et al.[23] concluded that "although the factors leading to accumulation of intra- and intermuscular fat (myosteatosis) are poorly understood, recent evidence indicates that increases in intramuscular fat are associated with disuse, altered leptin signaling, sex steroid deficiency and glucocorticoid treatment". However, the changes the authors describe (Fig. 4) are more extensive and seen in individuals who in the majority are much younger. Disuse of the extraocular muscle is almost impossible, and in their group of mild GO patients, no one had been treated with glucocorticosteroids. The presence of accumulating intramuscular fat, thus, seems to be part of the natural course of GO. While fatty degeneration in skeletal muscles might be related to loss of muscle strength, none of the patients in this study had diplopia or motility impairments. The impact of the fatty degenerations in the extraocular muscles, therefore, seems to be modest but could be of interest in patients with more severe manifestations of GO.

In conclusion, this and their previous studies show that in mild and untreated GO, the orbitopathy starts with extraocular muscle enlargement and clinical signs of inflammation. While these signs slowly disappear, a second phenomenon, namely neoadipogenesis, becomes apparent that stabilizes, but does not disappear, in the following 4 years. Moreover, fatty infiltration of the EOM seems to be part of the natural course of GO.

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