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MRI measurements of orbital tissues in dysthyroid ophthalmopathy

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The present work with human subjects has been performed in conformity with the Declaration of Helsinki, and informed consent has been obtained from all subjects. The experimental procedure was approved by the Ethics Committee of the Karolinska Institutet. The paper has not been previously published

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Abstract *Background:* Muscle volume investigation by different imaging techniques has proven useful in the diagnosis and follow up of treatment in dysthyroid ophthalmopathy. However, no study on muscle volume measurement by magnetic resonance imaging (MRI) has been done in this disease. *Methods:* Six patients with monocular or asymmetric binocular dysthyroid ophthalmopathy and eight controls were examined with orbital MRI using a surface coil. In the muscle volume study, 2 mm coronal slices were used for measuring the six extraocular muscles (EOM), i.e., medial rectus (MR), lateral rectus (LR) superior rectus (SR), inferior rectus (IR), superior oblique (SO), and inferior oblique (IO) muscles, as well as the orbital fatty tissue (OFT). In the muscle thickness study, 3 mm transverse and sagittal images were used for measuring the four rectus muscles during fixation in different gaze positions in horizontal and vertical planes. *Results:* In dysthyroid ophthalmopathy, the muscle volume of the six external eye muscles was significantly larger than in controls, except for the IO. The IR and MR showed the largest increase in muscle volume. The correlation between muscle thickness and different degrees of eye deflections was linear for all four rectus muscles both in patients and controls, and no significant differences in the slopes of the regression lines were found. The volume of OFT was significantly larger in patients than in controls, and the change in volume was larger than that of muscle volume. *Conclusions:* MRI technique makes it possible to observe and evaluate quantitatively the volume of all six extraocular muscles and the orbital fatty tissue in dysthyroid ophthalmopathy. It also makes it possible to evaluate changes in morphology during eye muscle contraction.

Introduction

It is well known that the extraocular muscles (EOM) are enlarged in dysthyroid ophthalmopathy. This can be easily observed by such imaging techniques as ultrasonography [5, 19], x-ray computed tomography (CT) [6, 7, 10, 11], and magnetic resonance imaging (MRI) [14].

Muscle volume investigation with CT has proven useful in diagnosis, prognosis, and follow up of treatment in dysthyroid ophthalmopathy [6, 7, 10, 11]. However, CT could not reliably distinguish rectus muscles from oblique muscles due to the low resolution and the artifact from orbital bone. Quantitative measurements of individual muscle volume with MRI have been used for evaluating muscle atrophy in patients with abducens and oculomotor palsy [4, 17], and muscle enlargement in patients with orbital myositis [17]. In a recent study, volume assessment of all six EOMs in normal subjects of different ages was reported [24]. In this study, it was found that the ranking order for the muscle volume (from largest to smallest) in normal subjects was superior rectus (SR), lateral rectus (LR) and medial rectus (MR), inferior rectus (IR), superior oblique (SO), and inferior oblique (IO). However, no study on muscle volume in dysthyroid ophthalmopathy has been done with MRI. Moreover, there is no study on measuring individual volume of all six muscles in dysthyroid ophthalmopathy. Increase in orbital tissue volume, leading to exophthalmos, could also be due to expansion of the orbital fatty tissue. Quantitative evaluation of orbital fat volume in dysthyroid ophthalmopathy has been done with CT [7] but not with MRI. Since MRI clearly shows OFT in the orbit due to its high signal intensity, it makes the OFT volume measurement accurate and easy.

Limitation of ocular motility is a common feature in patients with dysthyroid ophthalmopathy. Mechanical restriction has been proven by force duction test and by clinical findings of increased intraocular pressure during gaze in the defective direction. It also has been assumed that ocular motility disorder could be affected by paralysis of the agonist muscle due to damage to the eye muscle nerve [2], or to the inflammation of the muscles [9], or both. For studies of the contractile behavior of EOM, a kinetic imaging technique – cine MRI – has been used [1, 16]. In a recent study on a large group of normal subjects, a static mode of MRI was used to assess muscle contractile property in an indirect manner, i.e., the change of muscle thickness in different gaze positions [24]. It would be of interest to use this MRI technique for studies of the contractile properties of extraocular muscles in dysthyroid ophthalmopathy.

The aims of the present study are to: (1) clarify by volume measurements whether dysthyroid ophthalmopathy involves all six eye muscles, to what degree each muscle is affected, and if the orbital fatty tissue is involved; and (2) examine if eye muscles seem paralyzed in dysthyroid ophthalmopathy by studying the changes of muscle thickness related to the eye deviations.

Materials and methods

Subjects

MRI examinations were performed in six patients with monocular or asymmetric binocular dysthyroid ophthalmopathy and eight normal subjects. In the patient group were three males and three females aged 64±9.7 years (mean±SD). All had moderate or severe restrictions of eye movements. Details of the clinical findings are shown in Table 1. In the control group were three males and five females aged 63±4.6 years. All had full vision and normal eyes and ocular motility.

MRI scanning

The MRI device used in this study was a Siemens Magnetom SP63 (Siemens AS, Erlangen, Germany) operating at 1.5 Tesla. The orbital MRI examinations were performed with an orbital surface coil with an inner diameter of 3 inches.

Spin echo T1-weighted images were obtained. In the muscle thickness study, repetition time (millisecond)/echo time (millisecond)/field of view (millimeter)/matrix (TR/TE/FOV/matrix) was 350–522/22/130/256×128. In the volume study, TR/TE/FOV/matrix was 744–960/22/130/256×256. The size of the image voxel was approximately 1.5 mm^3 for the thickness study, and 0.5 mm^3 for the volume study. The slices were consecutive without gaps and cov-

Table 1 Clinical findings of patients (*LE* left eye, *RE* right eye, *Bil* bilateral, *VA* visual acuity, *Corr* correction, *pdt* prism diopter, *Vert* vertical, *Hori* horizontal, *Mac degen* macula lutea degeneration, *PP* primary position, *R/L* right over left hypertropia, *L/R* left over right hypertropia, *Eso* esotropia, *Exo* exotropia, *Abd* abduction, *slight, **moderate, ***marked)

Case	Age/sex	Affected eye	VA (Corr) RE LE	Deviation in PP (pdt)	Restriction of eye movement	Others signs	Phase of disease
1	72/M	LE	0.8 0.8	16 (R/L) 12 Eso	Up (to midline)	Lid edema* Redness* Chemosis**	Active
2	51/F	RE	0.4 0.8	30 (L/R)	Up (to midline)	Lid edema* Lid retraction*	Inactive
3	77/F	Bil More LE	1.0 0.5 Mac degen LE	2 (R/L)	Up (moderate) Abd (bil)	No	Inactive
4	68/M	Bil More RE	1.0 1.0	5 (L/R)	Up (moderate)	No	Active
5	59/F	RE	1.0 1.0	45 (L/R) 8 Exo	Up (to midline) Abd	No	Inactive
6	59/M	Bil More LE	1.0 0.9	No	Up (bil) (moderate) Abd (bil)	Lid retraction***	Inactive

ered the whole orbit. Detailed MRI parameters for scanning were given in a previous study [24].

In the muscle thickness study, the subject was asked to fixate at 19 gaze positions in horizontal and vertical directions. The horizontal fixations were done from the primary position to 30° adduction and 30° abduction in steps of 10°. The vertical fixations were done with the eye in 20° of adduction or abduction, from primary level upward and downward with the same range and steps as the horizontal fixations. A blinking mode of light targets was used during the fixation in order to attract the subject's attention. Details of a special setup with metal-free targets were reported previously [24]. For each gaze position, a series of six adjacent 3 mm thick image slices were obtained of both orbits by scanning for 48 seconds in the transverse plane and a series of 12 image slices by scanning for 70 seconds in the sagittal plane.

For muscle volume study, a series of 2 mm thick image slices were acquired in coronal plane, with a scanning time of 4–5 minutes. Since it was uncomfortable to hold fixation during such a long period, and fatigue-related eye movements might influence the image quality, the subject was instructed to close the eyes and try to maintain the eyes still at the primary position in order to minimize motion artifacts.

In the muscle thickness study, the orientation of the transverse slices was placed as parallel as possible with the medial and lateral rectus muscles. In the volume study, the coronal slices were orientated perpendicular to the anterior part of the optic nerves with the eye in the primary position of gaze. In muscle thickness as well as volume studies, sagittal slices were as parallel as possible to the superior and inferior rectus muscles.

Measurements

The images were magnified with an overhead projector and the projected image was measured against the scale on the MRI image to keep the proportions with the original image. The cross-sectional areas of the individual muscles, the optic nerve, and the eyeball were measured in sequential slices by tracing the outlines of the magnified images with a computer digitizer. The volume of each orbital tissue was calculated by adding up all the cross-sectional volumes of that tissue measured from coronal slices. Muscle thickness was obtained by measuring the thickest part of the muscle belly of transverse and sagittal slices.

Orbital fatty tissue was calculated by subtracting the volume of the all six extraocular muscles, the eye ball, and the optic nerve from the total orbital volume. Therefore, the orbital fatty volume includes the lacrimal gland, the vessels, and the other connective tissue, since these tissues are difficult to distinguish from fat.

Results

Enlargements of MR, IR, and SR were found in all cases. An enlarged MR of case 2 is shown in a transverse slice in Fig. 1. In this patient, the muscle volume was 2040 mm^3 in the affected eye and 590 mm^3 in the unaffected eye. Examples of the enlarged IR and SR in this patient are shown in Fig. 2. As a comparison, a sagittal slice from the eye of a normal subject is presented in Fig. 3.

In half of the patients, there was a marked enlargement of LR, and in two patients a moderate enlargement. Five of the six patients showed enlargement of SO. Clear enlargement of SO, SR, MR, and IR in the affected eye (right eye) of case 5 is showed in Fig. 4.

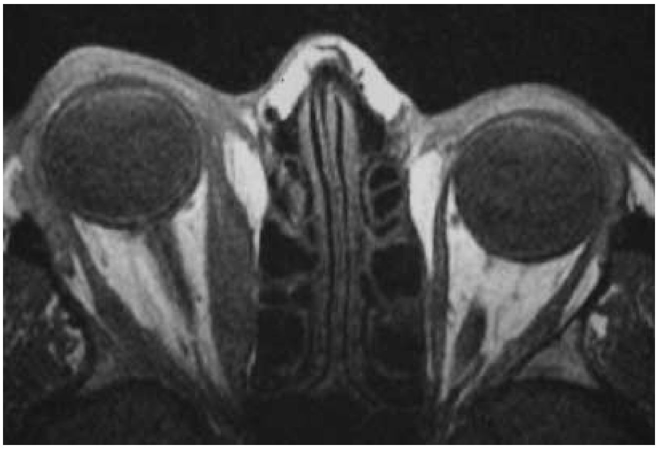


Fig. 1 A transversal slice from the right eye of a patient with monocular dysthyroid myopathy. The medial rectus (*MR*) is enlarged

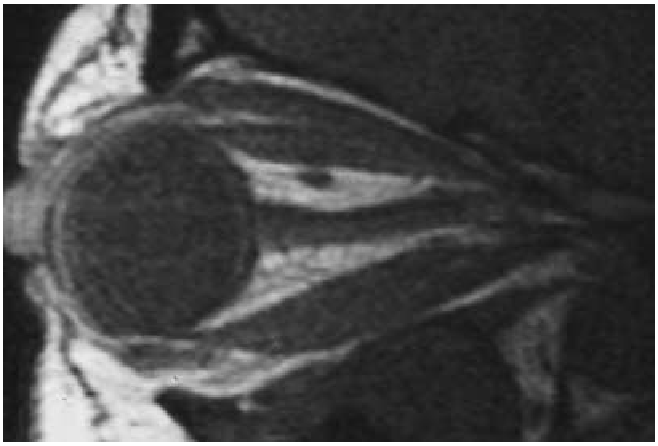


Fig. 2 A sagittal slice from the right eye of a patient with monocular dysthyroid myopathy. The complex of the superior rectus and levator palpebrae muscles (*SR*), and the inferior rectus (*IR*) muscle are enlarged

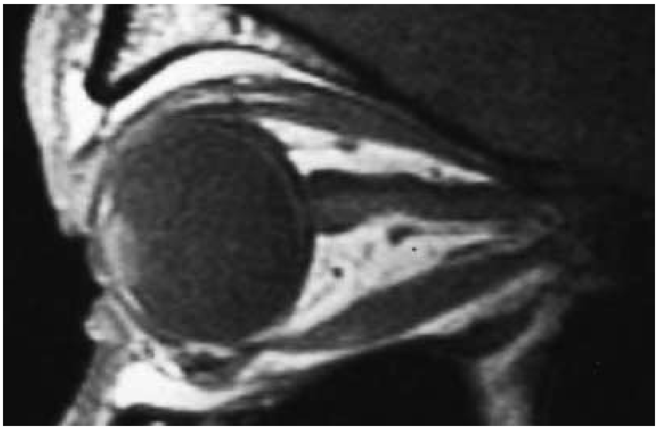


Fig. 3 A sagittal slice from the right eye of a normal subject

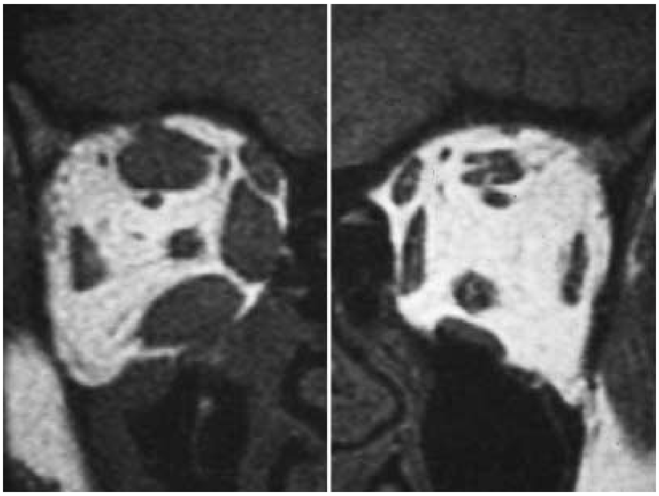


Fig. 4 A coronal slice from the right eye of a patient with monocular dysthyroid myopathy. The superior oblique (*SO*), superior rectus (*SR*), medial rectus (*MR*) and inferior rectus (*IR*) muscles are enlarged

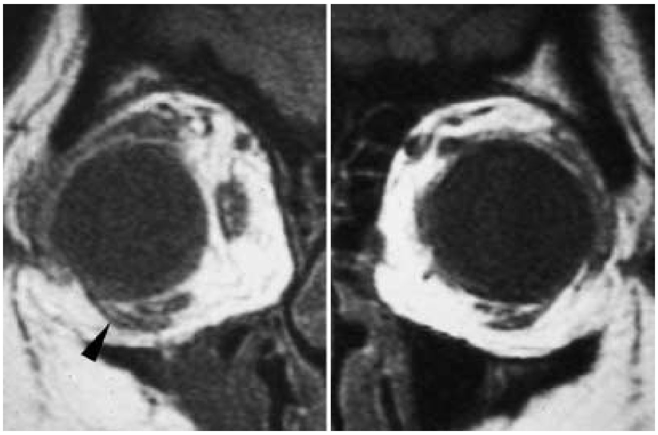


Fig. 5 A coronal slice from the right eye of a patient with inferior oblique muscle (*IO*) involvement. IO is enlarged (*arrow*)

In only one case (case 2)was the IO muscle found to be increased in volume compared with the value of the normal eye. Fig. 5 shows the enlarged IO muscle of the right eye in a coronal slice. In this case, the muscle volume of IO was 300 mm^3 in the affected eye (right eye) compared with 170 mm^3 in the unaffected eye (left eye).

Maximal thickness of eye muscles in different directions of gaze

The values of muscle thickness in the affected or more affected eye of patients were compared with those in the dominant eye of normal subjects.

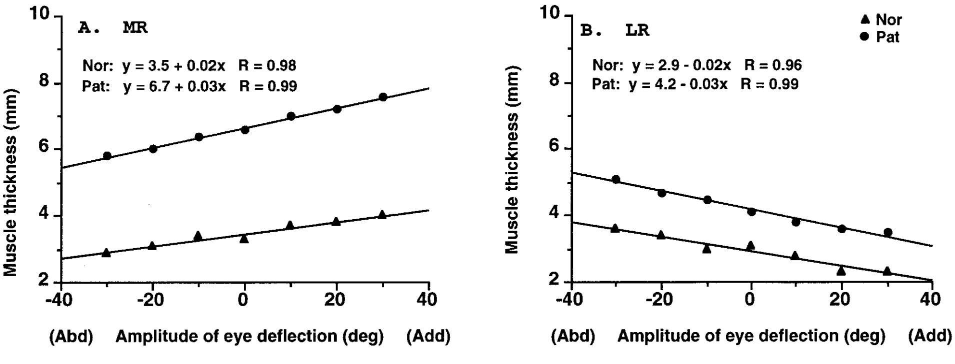
The mean values of maximal muscle thickness in different fixating positions over a range of 60^{o} of horizontal gaze are shown in Fig. 6A for MR and Fig. 6B for LR, together with the regression lines of the correlation analysis. The values of eye deviations over 60° of vertical gaze in the 20° abduction field of gaze are shown in Fig. 7A for SR and Fig. 7B for IR, and the values in the 20° adduction field of gaze in Fig. 7C for SR and Fig. 7D for IR. Linear correlations were observed for all four rectus muscles, both in patients and normal subjects. There were no significant differences in the slopes of the regression lines between the patients and the normal subjects.

The mean values of muscle thickness in different gaze positions were compared between the patients and the normal subjects (Student's *t*-test). The values in all gaze position for both horizontal and vertical rectus muscles were significantly higher in patients than in normal subjects.

Volumes of eye muscles and fatty tissue

The volumes for six extraocular muscles were compared between the patients and normal subjects (Student's *t*-test). All values from the eyes with dysthyroid ophthal-

Fig. 6A,B Mean values of maximal muscle thickness plotted against horizontal eye deflections in degrees. The regression lines are linear for the medial rectus (**A**) and for the lateral rectus (**B**), both in patients (*Pat*) and in normal subjects (*Nor*). (*Abd* abduction, *Add* adduction)



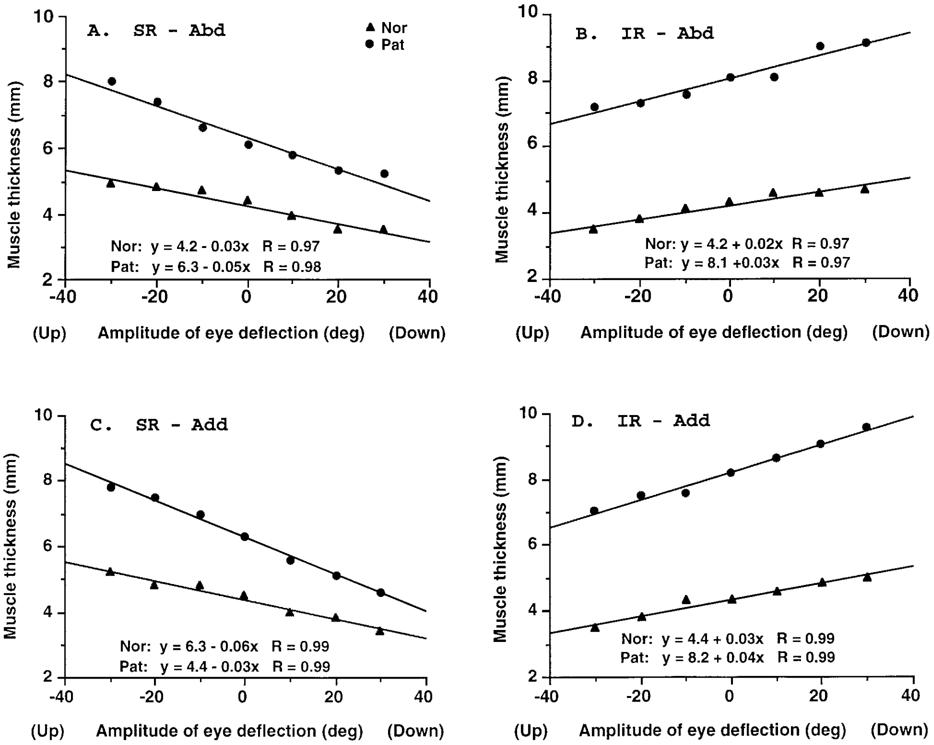


Fig. 7A–D Mean values of maximal muscle thickness plotted against vertical eye deflections in degrees. The regression lines are linear for the superior rectus in 20° abduction (**A**) and in 20° adduction (**C**) fields of gaze, and for the inferior rectus in 20° abduction (**B**) and in 20° adduction (**D**) fields of gaze, both in patients (*Pat*) and in normal subjects (*Nor*)

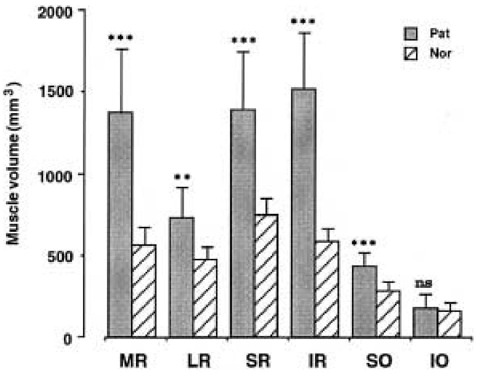


Fig. 8 Histogram of muscle volume (mean values) of the six extraocular muscles from both patients (*Pat*) and normal subjects (*Nor*). The *bars* represent one standard deviation. ** *P*<1%, *** *P*<0.1%, *ns* not significant

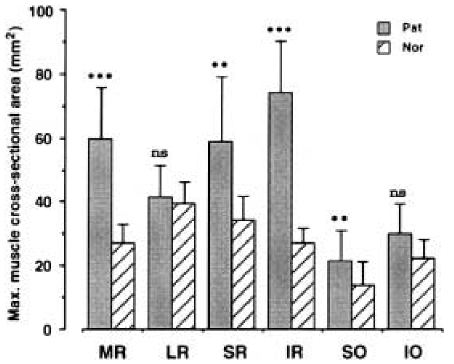


Fig. 9 Histogram of max. muscle cross-sectional area (mean values) of the six extraocular muscles from both patients (*Pat*) and normal subjects (*Nor*). The *bars* represent one standard deviation. ** *P*<1% *** *P*<0.1%, *ns* not significant

mopathy were significantly higher than those from normal subjects, with the exception of IO where only one patient showed an enlarged muscle. The mean values and standard deviations of the muscle volumes for all six muscles of patients and normal subjects are presented with histogram in Fig. 8.

The volume of orbital fatty tissue was also significantly increased in patients. In order to evaluate how the orbital fatty tissue and each muscle were involved in dysthyroid ophthalmopathy, a ratio was calculated between the volume values in patients and normal controls (Table 2). The highest ratios were found for IR (3.3) and MR (2.6), and the lowest for IO (1.1). Total muscle volume in patients was twice that of normal subjects. Although the ratio of the OFT volume increment was smaller than EOM, the amount of OFT increment was larger than EOM.

Maximal muscle cross-sectional area

The values of maximal muscle cross-sectional area of six extraocular muscles measured with coronal imaging at

Table 2 Mean values of muscle and orbital fatty tissue volumes, and mean ratios of the values between patients and normal subjects (*MR* medial rectus, *LR* lateral rectus, *SR* superior rectus, *IR* inferior rectus, *SO* superior oblique, *IO* inferior oblique, *TM* total muscle volume, *OFT* orbital fatty tissue, *Pat* patients, *Nor* normal subjects)

Orbital tissues	Volume (mm^3) at:	Volume (mm^3) Nor	Ratio of volume (Pat/Nor)
MR	1270	490	2.6
LR	730	490	1.5
SR	1220	600	2.0
IR	1370	420	3.3
SO	430	270	1.6
IO	180	160	1.1
TM	5200	2430	2.1
OFT	25080	21820	1.1

the primary position were also compared between patients and normal subjects (Fig. 9). Significant difference was found in MR, SR, IR, and SO, but not in LR and IO. However, significant muscle enlargement of LR was found in muscle volume measurements. The standard deviations of maximal cross-sectional area were generally larger than those of muscle volume.

Discussion

The most common ocular motility defect in dysthyroid ophthalmopathy is limitation of elevation of one or both eyes, followed in order of frequency by limitation of abduction [18]. The cause of the restrictions of movement has been discussed [3, 8, 15, 18, 21].

Marked resistance on passive elevation was found with the force duction test [15]. Length-tension measurements of detached muscles during surgery demonstrated an increased stiffness of the inferior rectus and medial rectus muscles in patients who had marked restriction of elevation and abduction [21]. Thus, the superior rectus was considered either essentially normal or with a pseudoparalysis, and the limitation of elevation was supposed to be due to myopathy and loss of elasticity of the inferior rectus. However, a paretic pattern of innervation of the superior rectus was found in an electromyogram (EMG) study in a patient with marked limitation of elevation [2], although this has been disputed by later reports [12]. It was also reported in a previous study that decreased saccadic velocity recorded with infrared technique and increased extraocular muscle volume measured by CT were correlated with the limitation of ocular motility [8]. However, no study on muscle measurement by MRI has been done in dysthyroid ophthalmopathy. MRI has some advantages compared to CT. First, the image contrast between of the soft tissue is higher in MRI than CT. Therefore, orbital tissues are delineated better. Second, any slice direction can be selected in MRI. Third, MRI can be performed without x-ray irradiation. Therefore, MRI allows each orbital tissue to be easily distinguished. Moreover, many trials of MRI study make possible the morphological study on contractile properties of horizontal and vertical muscles.

We previously have used the high resolution MRI technique in normal subjects and investigated the changes in muscle configuration during contraction by measuring muscle belly thickness at a series of gaze positions, both in the field of action (“on”), and out of the field of action (“off”) of the muscles [24]. We found that the larger the deviation of the eye into “on” field of the muscle the thicker the muscle belly, and the greater the deviation of the eye into the “off” field of the muscle the thinner the muscle belly. The correlations were found to be linear between muscle thickness and eye deviation. In the present study, a similar pattern of linear correlation was also found in patients. However, no significant differences were found in the slopes of the regression lines between patients and normal subjects, although the average values of muscle thickness were generally higher in patients than in controls. Thus, this morphological study on the dynamic changes of muscle thickness did not show any evidence of eye muscle paralysis in dysthyroid patients. Also, the contractile function in dysthyroid ophthalmopathy seems unaffected by the disease process, although intercellular sarcoplasmic disorganization was seen in biopsies from dysthyroid eye muscles [13]. The present findings were in accordance with our results of eye muscle force measurements in patients with dysthyroid ophthalmopathy, where increased isometric tension was found [23]. However, a more detailed study of muscle contractile properties using physiological methods is needed in order to further elucidate the muscle function.

It has been well established that muscle enlargement in dysthyroid ophthalmopathy is due to the pathological changes of myositis and muscle swelling [13, 20, 22]. Enlarged muscles can be easily observed by CT and MRI [6, 7, 10, 11, 14]. EOM volume previously has been measured with CT in patients with dysthyroid ophthalmopathy [6, 7, 10, 11] but not with MRI. In all these studies, the combined muscle volume of MR and SO, as well as IR and IO, was presented. Using high-resolution, surface-coil MRI with thin slices it is possible to separate rectus muscles from oblique muscles. So far, there has been no quantitative evaluation of which muscles are most involved in dysthyroid ophthalmopathy. We found that all the rectus muscles in the patients in our study were thicker than those in the controls at all gaze positions, especially for IR and MR.

By calculating the ratios between muscle volume of dysthyroid and normal subjects, we found that the most enlarged muscles were IR (ratio: 3.3) and MR (ratio: 2.6), which is in accordance with what we found in the muscle thickness study. All patients in our study had severe or moderate restriction of elevation, and three also had limitation of abduction, which would suggest that swelling of IR and MR may cause the clinical findings of eye movement limitations. Similar findings were reported in a previous CT study where muscle cross-sectional area and muscle width were measured [13], and the limitation of elevation and abduction seemed to be in relation to the enlargement of IR and MR.

The histopathological changes in dysthyroid ophthalmopathy consist primarily of inflammation of the extraocular muscles and the orbital fat [13]. However, a previous study with CT [7, 25] did not show any change in the absolute amount of orbital fat. In the present study, we found a significant increase of fatty tissue volume in patients with dysthyroid ophthalmopathy, but the relative change in volume was smaller than that of muscle volume, which was doubled in the patients on an average. However, in absolute values, the increment of OFT volume was larger than that of all EOM together, implying that OFT volume change is an important contributor to exophthalmos.

In summary, MRI technique will make it possible to observe and evaluate more quantitatively and more circumstantially than does CT the volume and thickness of EOM in dysthyroid ophthalmopathy. Of the six extraocular muscles, IR and MR showed the largest changes in muscle volume, and IO the smallest. Muscle thickness changed with eye deviation in the same way as in normal muscles, which did support the notion that the restriction of eye movement in dysthyroid ophthalmopathy may be due to mechanical restrictions by the enlarged antagonist muscles and not to paresis of the muscles. The orbital fatty tissue would also seem to be involved in the exophthalmos, and the change in volume was larger than in muscles alone.

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