

Ph.D. thesis

**MRI of the Orbit in Graves' Ophthalmopathy**

**Zsolt Szűcs Farkas, M.D.**

**Instructor: Endre V. Nagy, M.D., Ph. D**

**Department of Radiology**

**University of Debrecen Medical and Health Science Center**

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## 1. INTRODUCTION

Graves disease (GD) is an organ specific disease of the thyroid gland with an incidence of 5/100000 and a prevalence of 50/100000 in Hungary, accounting for the most frequent cause of hyperthyreodism.

The term Graves ophthalmopathy (GO) refers to the changes of intra- and periorbital soft tissues occurring in the course of autoimmune thyroid diseases. In some cases, GO may develop in euthyreoid state preceding other signs of hyperthyreoidism and eye- symptoms do not change parallel with thyroid function in the later stages of the disease as well.

The incidence of GO in Graves disease, depending on the diagnostic criteria, varies between 10-70%. It occurs more frequently in women, but men tend to develop more severe symptoms at a later age.

Despite the rapid progress in the number clinical studies focusing on GO in the last two decades, its pathogenesis is still not completely understood. The main causative agent in the thyroid gland is stimulating IgG autoantibodies against the TSH receptor (TRAb) which are responsible for the clinical symptoms of hyperthyreoidism and GD. The link between the thyroid and the orbital pathology is not clearly defined. In the orbit the cellular type immune process predominates; besides local cytokines (IL-2, IFN- $\gamma$ , TNF- $\alpha$ ) other factors (compression, disturbed orbital circulation) may play a role. The end result of these processes is the increase in production of strongly hydrophilic glycoaminoglycans (GAG). The consecutive edema with lymphocytic infiltration causes a significant swelling of the extraocular muscles, the (intra- and peri-) orbital fatty connective tissue and sometimes of the lacrimal gland. Because of the increased soft tissue volume, intraorbital pressure also raises which results in a forward displacement of the globe. More importantly, compression and tension of the optic nerve may threat with loss of vision. Recent studies presented evidence that not only edema but also a net tissue proliferation is present in GO, as preadipocyte fibroblasts in the orbital connective tissue and in the perimysium of the rectuses, due to local and circulatory factors, may mature into adipocytes.

Immunosuppressive drug- and radiotherapy may render the autoimmune process quiescent with near-normalization of muscle volumes. However, muscles frequently remain enlarged and dysfunctional muscles result in frank diplopia in many cases. In the latter process, fatty degeneration, collagen deposition and resultant fibrosis may play a role.

Smoking is a well known predisposing and facilitating factor in the development of GO. Patients with GD who smoke are more prone to have severe eye symptoms than non-smokers. As an underlying cause, direct irritative effects of smoke, consecutive alterations in the

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intraorbital circulation, changes of the number and antigen presentation of T-cells and of thyroglobulin level as well as alteration of the antioxidant system with an increased formation of antibodies are suspected.

Severity of eye-symptoms is only partly dependent on the activity of the autoimmune process. Besides common eye lid changes, extraocular muscle involvement is a characteristic feature of Graves' ophthalmopathy; CT studies report a muscle swelling in 40-70 per cent of the patients, in the acute phase with, later without edema. A usually bilateral proptosis is also present in 40-70 % of all cases.

Several classification systems of the eye changes in GO are known. The most wide spread one is the Werner/ATA (American Thyroid Association) classification which includes signs, soft tissue involvement, proptosis, extraocular muscle and corneal involvement and visual acuity as classes, graded by their severity [NOSPECS criteria].

Detecting activity of the inflammation in GO is crucial for selecting the most appropriate therapy. In the active stage of the disease, immunosuppressive medical treatment or radiation therapy may be indicated. In contrast, in the inactive phase these methods are to be avoided because of their side effects. Surgical decompression of the bony orbit or correction of the extraorbital muscles may be a therapeutic option also in the later stage; the only exception is the acute surgical decompression in very severe GO with imminent sight loss.

The judgment of therapeutic efficacy in Graves' ophthalmopathy rests to a large extent on improvement in the patients' clinical status. Unfortunately, clinical activity scores (CAS) based on symptoms fail to consistently provide reliable follow up data for therapy monitoring, and their use is limited. The elevated level of several parameters in the serum is neither characteristic for GO, nor for its severity. Urine GAG level measurements are not widely used in the clinical practice.

For patient follow-up in Graves' ophthalmopathy the most widely used imaging methods are sonography, CT and MR imaging. The accuracy of A- and B-mode sonography is less reliable because it requires unrestricted free gaze in several directions during examination, which is usually impossible due to eye muscle dysfunction in these patients. The method is also very examiner dependent and often fails to clearly visualize the orbital apex region. New generation CT scanners provide very thin slices in a subsecond time. The orbital components have different attenuation values so they can be well separated with CT; this is the reason for its wide use in orbital pathology. Muscle diameters and cross sectional areas can be also measured on CT scans. However, because of the risk of possible irradiation damage to the crystalline lens during repeated measurements, it is not suitable in the patient follow up. MR

imaging, with its own limitations such as cost and claustrophobia, obviates the use of ionizing radiation and is able to acquire cross-sectional scans in any desired plane. Elevated T2 relaxation time in extraocular muscles is considered as a sign of disease activity and used for monitoring of the effectiveness of therapy in GO. The most widely accepted gold standard for assessing inflammatory activity in GO is the detection and quantification of the somatostatin receptors on the surface of the activated orbital lymphocytes with  $^{111}\text{In}$  labeled somatostatin analogues (octreotid). However, this method is very costly and due to low spatial resolution it provides no data on the morphology of the orbital soft tissues.

In the later stage of the disease, decrease of the volume of the extraocular muscles and/or the connective tissue may indicate the success of the applied therapy. Direct volume measurement of extraocular muscles with MRI is not an easy task, requiring special computer analysis including applicable software and hardware, and valuable time from the radiologist. The usual approach to the enlarged eye muscles on MR- or CT images is that the examiner evaluates one or two diameter of each muscle. No consensus exists among radiologists in which plane these diameters should be measured. It has not been verified either, if muscle diameters or even cross sectional areas in any plane can actually substitute for the volume.

The increase in volume of the connective tissue and the extent to which this contributes to the expansion of extraorbital compartments and proptosis are not established in GO. It is also unknown whether smoking really has any influence on the volume of orbital soft tissue compartments at all, and if so, which compartment is affected at most.

## **2. AIMS**

**2.1.** We aimed to characterize the volume changes of the intra- and extraorbital compartments separately in GO by volume measurements with MRI. We also wanted to elucidate which tissue (muscle or connective tissue) contributes to a larger extent to proptosis.

**2.2.** We intended to clarify the grade of the volume shift of the fatty connective tissue from the intraorbital to the extraorbital compartment by comparing these volumes. It was also of our great interest, if connective tissue predominates in the total extraorbital soft tissue compartment in patients with proptosis.

**2.3.** We aimed to assess the reliability of the Werner score in the characterization of volume changes in GO.

**2.4.** To analyze the relationship between smoking and GO, smoking history of patients was compared with the volume of different orbital soft tissue compartments.

**2.5.** In an effort to find a reliable substitute for muscle volume in the patient follow up, different muscle parameters were compared with muscle volumes in the rectuses.

**2.6.** In order to reduce the image evaluation time, the possibility to perform these measurements for every rectus muscle in a single MRI slice was also studied.

**2.7.** We aimed to give a normal range for different orbital soft tissue parameters.

**2.8.** Our study group intended to find an inexpensive and rapid method to substitute for the costly octreotid scintigraphy for detecting inflammatory activity in GO.

### **3. PATIENTS AND METHODS**

#### **3.1. Characterization of extra- and intraorbital tissues with MRI**

During a one year interval, 70 orbits of 35 consecutive patients with GO (6 men, 29 women, age 28-79 years, mean age 49.3 years) and 40 orbits of individuals (5 men, 15 women, age 23-72 years, mean age 49.0 years) with no thyroid disease were studied in the Dept. of Radiology, Medical and Health Science Center, University of Debrecen. The patients had proven Graves' disease according to standard criteria and symptomatic GO, with or without diplopia, with no signs of optic neuropathy. MRI of both orbits has been performed in a conventional 1T MR unit (Shimadzu SMT-100X, Kyoto, Japan). Coronal, sagittal and axial non-contrast T1 weighted spin echo images (TR 500 msec, TE 15 msec, slice thickness 3 mm) were performed. Axial and sagittal planes were chosen to be parallel with the course of the optic nerve.

All scans were saved on compact discs. For image evaluation a computer program was used, which was developed in our laboratory for MR and CT image postprocessing purposes on a conventional personal computer using a Windows 95/98/2000/NT operating system. On the axial T1w scans rectus muscles, the intraorbital connective tissue (excluding the optic nerve), the borders of the bony orbit and that of the extraorbital soft tissue were outlined manually with the mouse by the same observer, who was unaware of any patient data except for name and age. A straight line connecting the lateral and the medial orbital rim was considered as the anterior border of the bony orbit, separating the intra and extraorbital spaces. Tissues lying between this line and the closed eyelids were considered as extraorbital in position. The superior and inferior border of the orbital space was the orbital roof and floor, respectively. In the knowledge of the pixel number of the enclosed anatomical object and the pixel size, areas were calculated and given in mm<sup>2</sup>. The measurements were repeated for every slices. The volume of a structure was given as the sum of the measured areas multiplied by slice

thickness. With this technique the volumes of the bony orbit, individual rectus muscles, the extraorbital soft tissue compartment and the extra- and intraorbital connective tissue were calculated. In many cases, it was impossible to clearly separate the levator palpebrae superioris and the rectus superior muscle from each other on the axial scans; therefore, these two muscles were assessed together.

The sum of the volumes of the intra and extraorbital soft tissues was considered as the total soft tissue volume. In an effort to find a parameter that best characterizes changes in patients, from these volumes seven ratios were calculated. The distance in mm between the cornea and a straight line connecting the lateral orbital rims, measured in an axial slice in the plane of the optic nerve and the crystalline lens, was considered as the grade of proptosis. The above mentioned orbital parameters were compared with the Werner- (NO SPECS) scores in patients in order to evaluate the influence of volume changes on clinical severity.

On the third coronal slice behind the posterior pole of the globe the cross sectional area ( $A_{meas}$ ), the long diameter ( $D_{long}$ ) and the perpendicular short diameter ( $D_{short}$ ) of the muscles were measured. Diameter perpendicular to the long axis of the muscle at the largest extent of the muscle belly (maximal diameter,  $D_{max}$ ) was also measured; in the transverse plane for the medial and lateral rectuses and in the sagittal plane for the superior and inferior rectus muscles. To assess if two diameters estimate volume more precisely than one, we hypothesized the coronal muscle projections to be regular ellipsoids and calculated an approximate cross-sectional area for each muscle as follows:

$$A_{calc} = (D_{long} \times D_{short} \times \pi) / 4.$$

To analyze the effect of smoking habits on the grade of exophthalmus and orbital volume changes, questionnaires were completed by every patient and by the control subjects. They were asked if they had smoked at the time of the MR examination or any time during their lives, and if so, how many cigarettes per day and for what duration of time they had smoked. Cumulative smoking (the total number of cigarettes smoked) was calculated as the product of cigarettes per day and smoking period in days.

Data analysis was performed with SAS for Windows 8.1 software package (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at a p value of 0.05 or less.

### 3.2. Comparison between $^{99m}\text{Tc}$ -DTPA SPECT and MRI

Fourteen adult GO patients (4 males 10 females) presenting bilateral exophthalmos with a clinical activity score (CAS) of 3 and above were selected for the study.

Every patient underwent the same MRI protocol as in 3.1., with an additional T2 relaxation time measurement in every rectus muscle on axial T2 weighted MR scans (TR= 2200 msec, TE= 90 msec, slice thickness= 3 mm).

The time interval between the MRI and SPECT was less than 10 days in any given patient. Orbital SPECT was performed in every patient using 7 MBq/kg  $^{99m}\text{Tc}$ -DTPA (PromtCarry, Szeged, Hungary), which was administered intravenously 30 minutes before imaging with a NUCLINE X-Ring (Mediso, Hungary) four-headed SPECT device. In one case, on a separate occasion, imaging was repeated after administration of 122 MBq  $^{111}\text{In}$ -Octreotide i.v. to the same patient.

After filtered back projection on the reconstructed 3D pictures, coronal, sagittal and transaxial slices were selected, covering the entire orbital (including retrobulbar) area. For analysis, nearly triangular regions of interest (ROI) were drawn on transaxial slices outlining areas corresponding to the right and left orbits. The outline of the left orbital ROI (OR ROI) was positioned over the temporal lobe of the right brain hemisphere to obtain a reference brain ROI (B ROI). Care was taken to exclude nasal and peripituitary activities. CPS (counts per secundum) values were registered. The CPS ratios as OR/B were calculated for each orbit in both transaxial and sagittal planes.

Comparison between MRI and SPECT result were performed in “active” and “inactive” orbits separately. Activity was considered if the T2 relaxation time in a rectus muscle reached 70 msec, which equals the mean +2SD value of normal individuals in a former study of ours on the same MRI unit. Each orbit was characterized by a MRI score, which equaled the number of active muscles in this orbit.

## **4. RESULTS**

### 4.1. Extraocular muscles

Except for the lateral rectus, the muscle volumes were significantly larger in the patient group than in the controls.

The calculated and measured cross sectional areas correlated well in every muscle in the Graves' ophthalmopathy group ( $r$  values between 0.914 and 0.966;  $p < 0.0001$ ), and somewhat weaker in the control group ( $r = 0.545-0.945$ ;  $p < 0.0001$ ). The long and short diameters in the

coronal plane correlated strongly with the coronal areas in the medial (RM), superior (RS) and inferior (RI) rectus muscles ( $r=0.842 - 0.896$ ;  $p<0.0001$ ), and less in the lateral rectus (RL) ( $r=0.613$ ;  $p<0.0001$ ).

In the RS and RI muscles, volume correlated best with the measured coronal area ( $T_{\text{meas}}$ ) ( $r=0.694$  and  $0.777$ , respectively;  $p<0.0001$ ). It is remarkable that, although maximal diameters were significantly larger in patients than in controls, they showed the weakest correlations with volumes in these muscles ( $r=0.530$  and  $0.679$ ;  $p<0.0001$ ). In contrast, maximal diameters exhibited excellent correlation with muscle volumes in the medial and lateral rectuses ( $r=0.868$  and  $0.869$ , respectively;  $p<0.0001$ ). The only other parameter showing a comparably high  $r$  value with muscle volume in the medial rectus was the coronal area ( $r=0.838$ ;  $p<0.0001$ ).

#### 4.2. Proptosis

Twenty-six orbits of 15 patients, in which proptosis was above the 90<sup>th</sup> percentile of the normal subjects ( $>20.5$  mm), were selected and analyzed separately (proptosis group). In four of these 15 patients proptosis was significant only at one side. Differences in volumes and volume ratios between this group of patients and controls were more marked than in the case of the GO group as a whole. For example, the total muscle / total soft tissue volume ratio, was 16% higher in the total GO group, but 34% higher in the severe exophthalmos group than in controls. The total connective tissue/total soft tissue volume ratio showed similar but less marked differences (2% and 5%, respectively). There was also a striking difference in the extraorbital soft tissue/bony orbit ratio (45% and 88% change to controls, respectively) along with a change in the grade of exophthalmos measured in millimeters (16% and 33% difference to controls, respectively). Patients without significant exophthalmos had less muscle and connective tissue volumes, both intra- and extraorbital, than patients in the proptosis group.

Both in patients with and without significant proptosis, the grade of exophthalmos showed a better correlation with connective and soft tissue volumes (in both cases,  $r=0.788$ ;  $p<0.00001$ ) than with muscle volumes (no significant correlation).

#### 4.3. Intra- and extraorbital connective tissue

No significant difference in the bony orbit volume between patients and controls was detected (23.23 and 23.31 cc, respectively). Patients possess a larger extraorbital connective tissue volume than normal individuals (1.88 and 3.20 cc, respectively;  $p<0.05$ ). Total soft tissue

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volume was also larger in the proptosis group than in controls and the proportion of the extraorbital connective tissue was also greater in them (18.9 and 11.9 per cent). Intraorbital connective tissue volume was larger in the patients with significant proptosis than in the control group (13.38 and 15.29 cc;  $p < 0.05$ ).

#### 4.4. Volumes and volume ratios in patients with different smoking history

Thirty of the 35 patients returned the questionnaires on their smoking habits. 16/30 patients were smoker at the time of the MRI, 8/30 were ex-smokers and 6/30 patients had never smoked (non-smokers). The total number of smoked cigarettes in the first two groups showed a wide variety between 7,300 and 620,500. The mean duration of smoking was 23.0 years (range 5-40 years). Interestingly, current smokers had significantly less extraorbital connective tissue volume (3.19 vs. 4.50 cc,  $p = 0.0018$ ), lower extraorbital connective tissue/extraorbital soft tissue ratio (27.0% vs. 33.1%,  $p = 0.008$ ) and lower extraorbital/total connective tissue ratio (17.6% vs. 22.5%,  $p = 0.020$ ) than patients who did not smoke at the time of the investigation. In contrast, we found that non-smokers had larger bony orbit volume (26.18 cc vs. 23.71 cc,  $p = 0.017$ ) than current- and ex-smokers assessed together. Total muscle/total soft tissue volume and total connective tissue / total soft tissue volume ratios in the smoking subgroups did not differ significantly.

Of the 24 current- and ex-smokers, 13 patients (22 orbits) had a severe exophthalmos. Data analysis showed that patients with severe proptosis had significantly larger extraorbital soft tissue volume and total muscle volume/bony orbit ratios as well as total connective tissue/bony orbit ratios than the ones without severe proptosis.

In the proptosis group, comparison between non-smokers (4/26 orbits) and current smokers together with ex-smokers (22/26 orbits) showed that non-smokers had a significantly larger total muscle, extraorbital soft tissue, extraorbital connective tissue and total soft tissue volume as well as greater proptosis and extraorbital connective tissue/total connective tissue, but no difference in the bony orbit volume was detected ( $p = 0.45$ ).

No relevant differences were detected in any measured volumes or calculated ratios in the control subjects grouped by smoking history. More importantly, non-smoker patients possess a larger bony orbit volume than non-smoker controls (26.2 vs. 22.9 cc,  $p = 0.0021$ ).

The number of smoked cigarettes correlated with numerous parameters, most importantly of all with total and intraorbital connective tissue volumes. A negative correlation was found with the muscle/total soft tissue ratio in ex-smokers, while muscle volume itself showed no correlation with cigarette consumption.

#### 4.5. Werner-score

The sum of the scores from the six classes of NO SPECS grading system for each eye, as an estimate for the clinical severity, correlated well with a series of different orbital parameters (total muscle volume,  $r=0.536$ ; extraorbital soft tissue,  $r=0.655$ ; proptosis,  $r=0.544$ ;  $p<.0001$  for each). Werner scores did not diverge significantly in the patient subgroups with different smoking habits and did not correlate with cumulative smoking but the scores from the left and right eyes in the same patient showed good correlation ( $r= 0.976$ ,  $p<.0001$ ).

#### 4.6. $^{99m}\text{Tc}$ -DTPA SPECT scintigraphy

In 9/14 patients no extraocular muscle edema was detected by MRI. In the other 5/14 patients, the MRI-score of the orbits was 1 or more. The orbit CPS/brain CPS ratio was  $8,30 \pm 2,08$  in the “active” orbits and  $6,40 \pm 1,17$  in the “inactive” orbits ( $p = 0,005$ ). Neither in the active nor in the inactive group was there side difference (left vs. right orbits) between the OR/B ratios ( $p>0.05$  in both groups). However, the difference was significant between the inactive and active patients’ groups OR/B values ( $p<0.05$ ). In a patient, who was not included in the above comparisons, both the  $^{111}\text{In}$ -Octreoscan and  $^{99m}\text{Tc}$ -DTPA intensively accumulated in the left orbital area.

### **5. DISCUSSION**

#### 5.1 Extraocular muscles

Although the involvement of extraocular muscles in GO is quite obvious, they are only less accessible for clinical examinations. CT has been used to characterize orbital soft tissues since the mid 1980s. American authors proved that volumes can be given as a product of the sum of areas measured in axial plane and slice thickness. They also provided a normal range for the connective tissue volume and the diameters of the extraocular muscles and that of the optic nerve.

MRI has been used only recently for volume measurements in GO in some experimental studies. The described automatized methods were applicable only in a quarter of patients. Measurements using 3D datasets are promising but this method requires special hardware.

If we use muscle volume as an outcome indicator of therapy, image postprocessing can be fairly time consuming for each follow up examination. With repeated assessment of an easy-to-measure parameter that correlates well with muscle volume changes, this time could be significantly reduced. The coronal is the only plane in which all rectus muscles can be

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visualized on the same slice. Extraocular muscles are cylindrical objects, with a narrowing at their origin at the ligament of Zinn in the orbital apex and, similarly, their front ends become thinner as they approach their insertion at the equator of the globe. Therefore, their coronal cross sections, which are nearly ellipsoids, could be ideal candidates for evaluation in the midorbital region. For this reason we have chosen consistently the same slice 9 mm posterior to the globe in every study subject.

Upon measurements in 440 rectuses we found that, although the above mentioned coronal scan may or may not intersect the muscles at their greatest extension, long and short diameters and coronal areas correlate better with muscle volume than maximal diameters do, at least in the superior and inferior rectuses in the Graves' ophthalmopathy group. Volume of the medial rectus can be also well estimated by the cross-sectional area measured on the same slice. In the case of the lateral rectus muscle we think it best to estimate muscle volume changes on the basis of the greatest diameter measured in the transverse plane. So, these parameters may be well used as a substitute for muscle volumes in the follow up of patients with GO.

In the RS, RI and RM muscles, short and long diameters measured in this coronal may be used as an alternative to estimate muscle volume in patients. The excellent correlation between the measured and the calculated areas for every muscle in the patients indicates that the cross-section of the enlarged muscle is almost a regular ellipsoid, the area of which can be well estimated by measuring its long and short diameters. In contrast, normal sized muscles of control individuals, especially the medial rectus, often exhibit an almost crescent shaped or irregular coronal projection that can be responsible for the weaker correlations. In general, one coronal diameter signals volume changes less reliably than having both diameters measured, which is also a consequence of the ellipsoid shaped coronal projection of enlarged muscles.

It is not clear if changes occurring in muscle shape and length after therapy have a significant influence on the use of the above mentioned correlations. To answer this question further prospective follow-up studies among patients with Graves' ophthalmopathy are required. Long-term clinical studies are necessary to ascertain correlation between volume and function of extraocular muscles.

### 5.2 Differences in the proptosis group

The grade of proptosis in a normal population is dependent on several factors, including ethnic group of origin and measurement technique. In order to study the contribution of volume changes in different orbital compartments to proptosis, orbits showing exophthalmos

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larger than 20.5 mm (which was the ninetieth percentile of our control group) were considered as significant and this group of patients was analyzed separately. This proptosis group had a larger total muscle (+63%), extraorbital soft tissue (+79%) and extraorbital connective tissue volume (+82%) than the normal subjects.

There was also a significant difference in a series of parameters between patients with and without proptosis. The fact that both muscle and connective tissue volumes were larger in the proptosis group than in the non-proptosis group indicates that increase in both compartments contribute to exophthalmos, though total muscle volume did not show a significant correlation with proptosis in either group.

A unique finding in our study is that extraorbital connective tissue of patients was disproportionately more expanded than intraorbital connective tissue. In contrast, within the confines of the bony orbit, muscle enlargement appeared to predominate over connective tissue changes in virtually every subgroup of patients. However, due to the larger amount of connective tissue in the orbit (approx. 3-4 fold larger volume than that of extraocular muscles), connective tissue volume change is considered an equal contributor to orbital content expansion in patients with GO, if their smoking history is disregarded. Based on these findings, one may speculate that muscle volume expansion in the orbit is accompanied by comparable changes in connective tissue volume, and, due to limited space within the bony orbit, the eyeball is shifted forward. Concurrently, there is a shift of the intraorbital connective tissue towards the extraorbital compartment. This supposition is further supported by the finding that the severity of proptosis correlated better with extraorbital and total soft tissue volumes than with any of the muscle volumes.

In patients with more severe exophthalmos, a larger part of the globe, extraocular muscles and lacrimal gland are protruding, causing an increase in extraorbital soft tissue volume and decreasing the relative percentage of connective tissue in this compartment. In acute inflammation, a swollen eyelid may also play a role.

We observed a clear contrast between patients without proptosis and controls regarding their intra- and extraorbital changes. On the one hand, there was a significant difference in the extraorbital connective tissue and in extraorbital soft tissue volumes in favor of the non-proptosis patients' group. On the other hand, virtually no alteration was detected in the total muscle volume and intraorbital connective tissue volumes. These data raise the question if the inflammatory process in mild forms of GO confines solely to or it is much more expressed in the extraorbital compartment. Alternatively, these findings can be interpreted as a remnant of

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chronic inflammation, where the intraorbital swollen tissues regained their normal sizes while extraorbital tissues remained permanently affected.

### 5.3 Differences in the smoking subgroups of patients

In the study design we hypothesized that smoking might have an influence on the grade of volume increase of different orbital compartments and might also alter the proportional change of these tissue spaces to each other.

Perhaps, the most surprising finding was the clearly larger volume of bony orbits in non-smokers compared to current- and ex-smokers assessed together, without significant difference in the muscle and connective tissue volumes. There was also no difference in the bony orbit volume in non-smokers with and without proptosis, as well as between non-smokers and current smokers or ex-smokers in the proptosis group. Upon these data, it can be conceived that non-smokers are less apt to develop severe eye-symptoms and proptosis because, having a larger bony orbit volume, intraorbital soft tissues have more space to expand during the inflammation, so the same volume increase leads to clinical symptoms in them later than in current smokers who possess smaller orbits. The trend toward smaller percentage of intraorbital connective tissue, despite the marginally elevated total soft tissue volume in non-smokers, may further support this theory. In the proptosis group, difference in the bony orbit volume between non-smokers and current- and ex-smokers disappears, maybe as a consequence of the explicit volume expansion, which may lead to a consecutive impression on the medial orbital wall. This phenomenon appears as a usual MR feature at advanced stage of GO, namely, the thin medial wall of the bony orbit as a locus minoris “outpouches” in the medial direction and fills up with fatty connective tissue, resulting in a larger orbital volume.

We found no significant difference in the bony orbit volume of the smoking subgroups in the control subjects, but non-smoker patients proved to have larger bony orbit volume than non-smoker controls. Although non-smoker patients also possess larger muscle volume, extraorbital- and total connective tissue volumes than non-smoker normal individuals, the muscle/bony orbit ratio as well as the grade of proptosis showed no difference between the two groups. Meanwhile, unlike non-smoker patients, current- and ex-smoker patients have larger proptosis, volumes, and corresponding ratios than controls in virtually all compartments. This might indicate that the orbital inflammation in GD differently affects patients with or without smoking history. The fact that in the control group smoking did not affect the volume of the bony orbit supports the notion that the lack of smoking history alone

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does not lead to a larger orbital volume. It is rather the soft tissue expansion in GO which, in non smokers only, somehow expands the bony orbit, preventing from crowding and developing serious symptoms.

In current smokers, cumulative smoking correlated well with intraorbital, but not extraorbital, connective tissue volume. Because this tissue occupies a large portion of the bony orbit (above 60%), consecutive alterations in the total connective and soft tissue volumes occur. These findings may support the result of some recent experimental studies that smoking might facilitate adipogenesis and volume increase of fatty connective tissue in GO, although distinguishing between edematous swelling without net proliferation and true adipogenesis with increase in number of cells is not possible with conventional MR imaging.

In ex-smokers, the amount of extraorbital connective tissue but not that of extraorbital soft tissue correlates well with cumulative smoking. It is not clear, why smoking does not correlate with extraorbital connective tissue in current smokers. In the ex-smoker subgroup, probably the volume increase of the intraorbital connective tissue (which is not related to the severity of smoking) causes a consecutive reduction in the muscle/total soft tissue ratio, as total connective tissue/total soft tissue ratio slightly rises. A direct effect on muscles, for example, fibrotic shrinking in the late phase of the disease can also not be excluded, since patients with smoking history possess less total muscle volume and smaller muscle/total soft tissue volume ratio than non-smokers. To explore the possible mechanisms responsible for this finding, additional studies are necessary.

#### 5.4 Werner-score

The Werner-score of the eyes showed a correlation above 0.5 only with the extraorbital soft tissue volume, proptosis and with total muscle volume. This means that the Werner score system for clinical severity is restricted to the estimation of these parameters, and gives little information on the changes in total connective tissue volume and intraorbital connective tissue volume, although these are the largest orbital compartments. The score, while alterations in volumes of numerous orbital components were remarkable, showed no significant difference in smoking subgroups, further supporting our observation that the Werner score is not closely related to volume changes.

#### 5.5 Comparison between $^{99m}\text{Tc}$ -DTPA SPECT and MRI

Up to now, water content of the muscles, as judged by the relaxation times of T2 MRI images has been widely used for the estimation of disease activity in the extraocular muscles of GO

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patients. Although attempts had been made to find a radiopharmaceutical which could detect disease activity in GO, the only suitable method was  $^{111}\text{In}$ -Octeroscan scintigraphy with a 90 % positive and a 100% negative predictive value. Unfortunately, due to cost reasons, it failed to become a widely used technique.

Theoretically, the  $^{99\text{m}}\text{Tc}$ -DTPA complex, administered intravenously shows correctly the high capillarisation of any inflammation site and, leaving the vascular bed through damaged capillary walls, “leaks out” into the interstitial fluid and bounds to polypeptides which are present in the extracellular fluid at inflammation sites.

Our results show, that  $^{99\text{m}}\text{Tc}$ -DTPA SPECT is suitable both for imaging and quantitative estimation of disease activity in GO. As far as imaging, resolution and muscle size information are concerned, the superiority of MRI remains unquestionable. But in addition to an MRI at diagnosis, repeated  $^{99\text{m}}\text{Tc}$ -DTPA scans can influence treatment decisions and measure the effectiveness of immunosuppression in GO. Major advantages of the  $^{99\text{m}}\text{Tc}$ -DTPA scan are low time consumption, low radiation exposure to the patient, low cost, and simple evaluation process. The limited number of patients in our study did not allow us to test specificity; we hypothesize that, in the detection of disease activity, it has the same specificity as  $^{111}\text{In}$ -Octreoscan. This finding support the results of former studies, which emphasize the possibility of other mechanisms than specific receptor binding (most of all venous hyperemia) in octreotid scintigraphy. Further studies on larger numbers of patients may find the exact role of this method among other imaging techniques in GO.

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## 6. NEW FINDINGS

**6.1.** Besides T2 relaxation time measurements for estimation of disease activity, monitoring of volume changes of orbital soft tissues is necessary in the follow up of patients with GO.

**6.2.** Based on volumetric MRI measurements we gave a possible normal range for the volume of bony orbit and for several parameters of the extraocular muscles.

**6.3.** In patients with Graves' ophthalmopathy the volume of the superior, medial and inferior rectus muscles, can be accurately estimated by simple measurement of their cross sectional area in a properly chosen coronal MR slice. The largest transverse diameter in the lateral rectus can be used for the same purpose.

**6.4.** Acquisition of the long and the short diameters in a proper coronal slice can be an alternative for the coronal area in the three most frequently enlarged muscles (RS, RI, RM). Deduction of muscle volume from one single coronal diameter is generally not advisable.

**6.5.** We proved with volume measurements that swelling both of the rectus muscles and the orbital fatty connective tissue, although to a slightly different degree, play a role in developing proptosis.

**6.6.** Non-smoker patients with GO have a larger bony orbit than smoker patients or non-smoker controls. The larger volume of the orbit may be protective against developing severe eye symptoms.

**6.7.** Cumulative smoking correlates with the volume of the intraorbital connective tissue in current and ex-smoker patients. Smoking severity does not correlate with the total muscle volume.

**6.8.** In GO without significant proptosis the inflammatory process may confine to or be more pronounced in the extraorbital compartment.

**6.9.** The Werner score based on the NO SPECS criteria provides no reliable information on the volume changes in the orbit.

**6.10.** Orbital uptake of  $^{99m}\text{Tc}$ -DTPA measured with SPECT correlates well with the severity of inflammation on MRI. This promising method seems to be suitable to assess disease activity in GO and may replace the costly Octreotid scintigraphy in the future.

**Scientific publications used in the Ph.D. thesis:**

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