Research Paper
Imaging

Semi-automatic magnetic resonance imaging based orbital fat volumetry: reliability and correlation with computed tomography

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Abstract. Post-processing analysis can provide valuable information for diagnosis and planning of orbital disorders. This cross-sectional study aims to evaluate the reliability of semi-automatic, orbital fat volumetry using magnetic resonance imaging (MRI). Two observers assessed the orbital fat volume using a standard MRI protocol (3T, T1w sequence) in 12 orbits diagnosed with Graves' orbitopathy (GO) and 10 healthy control orbits. MRI and computed tomography (CT) based analysis were compared. Intra-observer variability was good (intraclass correlation coefficient (ICC) 0.88; 95% confidence interval (CI) [0.70, 0.95]) and interobserver agreement was moderate (ICC 0.55; 95% CI [−0.09, 0.81]), which corresponds to a mean percentage difference of 1.3% and 17.9% of the total orbital fat volume. Mean differences between MRI and CT measurements were, respectively, 1.1 cm³ ($P=0.064$, 95% CI [−0.20, 2.43]) and 1.4 cm³ ($P=0.016$, 95% CI [0.21, 2.56]) for the control and the GO group. MRI volumetry was strongly correlated with CT (Pearson's $r=0.7$, $P<0.001$). We conclude that orbital fat volumetry is feasible with a semi-automatic segmentation procedure and standard MRI protocol. Correlation with CT volumetry is good, but considerable bias may derive from observer variability and these errors should be taken into account for the purpose of volumetric analysis. Better definition of error sources may increase measurement accuracy.

Key words: computed tomography; magnetic resonance imaging; Graves' Orbitopathy; orbit; computer-assisted image processing.

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Orbital fat involvement is a characteristic feature and has been widely studied in patients diagnosed with inflammatory eye diseases, such as Graves' orbitopathy (GO)^{1,2}. Fibroblast proliferation and adipogenesis increase soft tissue volume in the orbital cavity, contributing to proptosis and periorbital swelling, potentially leading to optic nerve compression³⁻⁵. In GO patients, the amount of the volume increment of orbital fat is much larger than that of the extraocular muscles with the degree of exophthalmos being significantly related to orbital tissue increase^{2,6}. Measurement of orbital fat can be used as an early marker to assess disease severity, activity and to monitor effectiveness of therapeutic modalities over time^{2,7-9}. Therefore, orbital imaging is a valuable tool to support the diagnostic pathway, during follow-up or prior to surgery in patients with GO^{8,10}. Post-processing of radiological images allows for objective detection of changes in orbital tissue volume. Accuracy of morphometric measurement depends on the correct identification of intensity difference between the targeted volume and its surrounding tissues. Monitoring orbital fat volume is a challenging task because it has no defined shape of its own and merely fills the spaces between the better-defined tissues (e.g., eyeball, extraocular muscles and optic nerve)².

Consensus on the use of different imaging modalities has yet to be reached⁸. Computer tomography (CT) was always considered the gold standard for surgical planning due to the clear visualization of the bony orbit, fat and muscle tissue. Pre- and postoperative CT volumetric studies have been successfully used for the assessment of orbital decompression surgery^{8,11}. CT has been used to quantify the volume of extraocular muscles and orbital fat in GO^{12,13}. Serial CT imaging, however, can cause radiation-induced cataract and lens opacifications, limiting its clinical use in long-term follow-up of eye diseases^{9,14}. Magnetic resonance imaging (MRI) provides excellent soft-tissue contrast, with better delineation of the orbital tissues and MRI can yield images in any plane. With the increasing use of MRI for evaluating GO, various protocols are described for safe and accurate measurement of adipose tissue with MRI^{7,9,14-16}. Initially, only determination of two-dimensional measurements was feasible, but technological advances and software-assisted volumetric measurement facilitated the process for three-dimensional analysis^{7,9,17}. Different segmentation techniques have been developed to define the tissue borders and allow quantitative

analysis. Due to the irregular morphology of orbital fat, the manual segmentation (i.e. tracing the tissue on each consecutive scan) is time-consuming and associated with high inter-operator variation^{16,18}. Semi-automatic segmentation techniques try to address these issues, as the software will define the tissue outlines depending on reference tissue intensity. These semi-automatic techniques still need a variable level of manual adjustments, depending on the image quality and properties of the studied tissue.

If fat volume is to be used as an indicator for diagnosis and treatment of orbital disorders, it is important that correlations between CT and MRI measurements are transparent and that the errors implicit in the measurement technique are defined. Currently it is not clear whether findings from one imaging technique can be translated to another. Furthermore, orbital imaging with CT or MRI can be useful at different stages during follow-up of the same patient. It would add great value to interpret disease evolution if results from both scans would be comparable. The measurement protocol should be easy to perform in routine clinical practice and involve post-processing software with a short learning curve. The aims of this study are (1) to analyse whether it is feasible to use a standard MRI protocol and a semi-automatic segmentation technique to measure orbital fat volume in routine clinical practice and (2) to find out to what extent the results from MRI fat volumetry are comparable with a CT-based analysis.

MATERIAL AND METHODS

Data collection

In this retrospective, cross-sectional study, 12 orbits of six patients (three female; mean age 55 ± 16 years) diagnosed with GO were consecutively selected between January 2017 and December 2018. All patients were evaluated in an inactive disease stage according to the EUGOGO guidelines²⁰. Patients were only included if they received both orbital CT and MRI scan as part of routine follow-up, with a maximum of 3 months between both scans (mean interval 8 ± 10 days). For all cases, CT scan was performed for surgical planning of an orbital decompression procedure. Additionally, five control patients (two female, mean age 44 ± 14 years) with 10 healthy orbits were randomly selected. Imaging was performed in the context of head trauma ($n = 2$) or cerebral intervention ($n = 3$). Patients were includ-

ed if they were 18 years or older, received both orbital CT and MRI scan with a maximum of 3 months interval (mean interval 16 ± 18 days). The exclusion criteria were: orbital and ocular pathology; previous ocular and periocular surgery; orbital trauma; previous radiotherapy in head and neck region; long-term use of systemic corticosteroids; and CT scans showing motion artifacts. The study adhered to the tenets of the declaration of Helsinki. Institutional review board approval and informed consents were obtained (B670201733474).

Scan protocol

GO patients and controls were scanned with current clinical standard of care protocols. Non-contrast-enhanced, T1-weighted images were obtained on a 1.5T or 3T MRI (Siemens Magnetom AVANTO or PRISMA) in axial (TE: 2.78–7.8 ms; TR: 251–356 ms) and sagittal planes (TE: 2.51–7.8 ms; TR: 255–649 ms) with standard head coil. Continuous slices of 3 mm thickness were obtained. Patients were instructed to keep their eyes closed and adopt a neutral position of gaze during scanning. All CT scans were obtained through the multidetector technique with a field of view containing the orbital structures (Siemens Somatom AS). A single volume of data was acquired in the axial plane at 1–2 mm thickness. All non-contrast-enhanced images were recorded in Digital Imaging and Communications in Medicine 3.0 (DICOM) format, anonymized and transferred to a workstation for analysis.

Orbital fat segmentation and volume measurements

Fat volume assessment on MRI was performed on a commercially available post-processing software package: Oleasphere (v3.0, Olea Medical, La Ciotat, France). The orbital fat volume of both eyes was measured on a workstation using a 21.3-inch flat-panel color-active matrix thin-film-transistor medical display (Nio Color 3MP, Barco, Kortrijk, Belgium) with a resolution of 2048×1536 at 76 Hz and 0.2115 mm dot pitch operated at 10 bits. Two observers were trained and calibrated to analyse the orbital MRI scans of 22 orbits. To do so, they were permitted to use enhancements and orientation tools such as magnification, brightness, and contrast to improve visualization of the landmarks. Each assessment required 15–30 min. The Oleasphere software allowed for a semi-automatic, threshold-based seg-

Fig. 1. Segmentation and volumetric analysis of the orbital fat. (A) Axial slice of an orbital magnetic resonance imaging (MRI) scan (T1w, non-contrast-enhanced) at the level of the optic nerve. (B) Orbital fat segmentation (green) using a semi-automatic, threshold-based technique. (C) Three-dimensional reconstruction of an orbital computed tomography scan with facial skeleton (pink) and orbital fat volume (purple and yellow) using Mimics Medical 21.0 software. (D) MRI-based 3D reconstruction of the segmented orbital fat tissue. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

mentation of different orbital structures. The orbital region of interest was obtained by manual delineation of the orbital cavity on each slice that contained orbital structures. The anterior border of the orbital cavity was delineated by the anterior lacrimal crest, frontozygomatic suture, inferior orbital rim and frontal bone. A threshold based, region grow algorithm was used to segment the orbital fat tissue and excessive components (e.g., fatty orbital bone marrow) were manually erased on each slide. Segmentation was performed on the axial slices, with visual control in the other orthogonal planes. After segmentation, the Oleasphere software automatically calculated the fat volume.

Fat volumetry on CT images was conducted according to the validated protocol by Regensburg and colleagues¹². DICOM files were uploaded into Mimics Medical 21.0 (Materialise, Leuven, Belgium). Contrast was adjusted for optimal visualization of the orbital fat. The orbital fat was identified using a multi-dimensional threshold-based segmentation method with the possibility of manual adjustment on each slide. A three-dimensional recon-

struction of the orbital fat was generated and saved as a stereolithography (STL) file. The software automatically calculated the fat volume. Fig. 1 shows the segmentation and volumetric analysis of the orbital fat.

Variability analysis

Two observers (B.D., R.W.) with a variable level of expertise (respectively, junior radiologist and head and neck surgeon) were blinded to the patients' clinical condition and independently performed the volume measurements. One observer (R.W.) repeated the procedure twice on different occasions to study the intra-observer variability. Right and left orbit were examined separately.

Statistical analysis

The data were analysed using MedCalc statistical software (Version 12.0, Ostend, Belgium). Means and standard deviations of orbital fat volumes were calculated for each observer separately. For inter- and intra-observer variability tests, the intraclass correlation coefficient (ICC) with

95% confidence interval (CI) was calculated (two-way mixed-effects model). The ICC is interpreted as follows: value of 1 indicates perfect agreement; values of >0.9 are considered ideal to be used in a clinical setting. Values of $0.75-0.9$ represent good agreement, <0.75 and ≥ 0.5 is moderate, and <0.5 is poor reliability^{21,22}. Orbital fat volumes on MRI scans were compared with CT scans using a paired Wilcoxon signed rank test. A Mann-Whitney *U*-test was used to compare the control and GO group for difference between MRI and CT volumetry. The Bland-Altman method was used to calculate the mean difference and to evaluate the 95% limits of agreements between fat volume measurements by CT and MRI²³. Pearson correlation was calculated to study the correlation between the mean fat volume on MRI and CT. Mean, median and 95% CIs were calculated when appropriate. Differences were considered statistically significant at $P < 0.05$.

RESULTS

Two trained observers analysed the orbital MRI scans of 22 orbits. The mean orbital

Fig. 2. Results of orbital fat volumetry on computed tomography (CT) and magnetic resonance imaging (MRI) for Graves' orbitopathy (GO) and control orbits. Means (with 95% CI (confidence interval)) and medians are provided.

Table 1. Reproducibility testing for orbital fat volume measurements on magnetic resonance imaging.

Orbital volume ^a (cm ³)	Observer 1	Observer 2	ICC (95% CI)
Interobserver variability	8.5 ± 2.0	10.3 ± 2.4	0.55 (-0.09; 0.81)
Intra-observer variability		Observer 2a 10.3 ± 2.4	Observer 2b 10.3 ± 2.1 0.88 (0.70; 0.95)

CI, confidence interval; ICC, intraclass correlation coefficient, outcome values: 0 = no agreement, 1 = perfect agreement.

^a Variables are denoted as mean ± standard deviation.

fat volume in the control group was 9.1 ± 1.9 cm³ on MRI scan compared with 10.2 ± 2.2 cm³ on the CT scan (mean difference 1.1 cm³, $P=0.064$, 95% CI [-0.20, 2.43]). The volume measurements for the GO group were, respectively, 10.3 ± 1.6 cm³ and 11.7 ± 2.1 cm³ on MRI and CT scans (mean difference 1.4 cm³; $P=0.016$; 95% CI [0.21, 2.56]) (Fig. 2). The mean difference between CT and MRI volumetry in the control group was not significant (Supplementary Table S1) when compared with the GO group ($P=0.722$; 95% CI [-1.37, 1.06]).

The ICC values for orbital fat measurement are presented in Table 1. Intra-observer variability was good (0.88; 95% CI [0.70, 0.95]; $P<0.001$) and interobserver agreement was moderate (0.55; 95% CI [-0.09, 0.81]; $P=0.38$). This represents an absolute mean difference of, respectively, 0.13 cm³ and 1.72 cm³, corresponding to a mean percentage volume difference of 1.3–17.9%.

Fig. 3 illustrates the correlations between orbital fat volume measurements by MRI and CT. There is a strong positive linear correlation between the mean fat volume measurements on MRI and CT ($r=0.7$, $P<0.001$). The Bland–Altman plot (Fig. 4) illustrates the mean difference of

orbital fat volume measurement between CT and MRI (mean difference 1.3 cm³; 95% CI [0.58, 2.07]). Relative to the mean orbital fat volume, this value corresponds to a mean percentage volume difference of 12%.

DISCUSSION

Advances in orbital imaging and post-processing techniques with MRI and CT scans provide objective measurements to support diagnosis and treatment in orbital diseases. CT and MRI scans both have distinct characteristics, but the use of MRI is increasing, especially when sequential imaging is needed in chronic disorders. Extensive heterogeneity in the use of different imaging modalities and highly demanding, time-consuming protocols, however, hamper the routine clinical implementation and make comparison of results difficult. If measurement of orbital fat could contribute to the routine management of orbital disorders, it is paramount to study the feasibility of fat segmentation based on standard orbital MRI scans and investigate the agreement with the CT measurements.

This study illustrates that a standard, T1 weighted orbital MRI scan can be used to

estimate the orbital fat volume. A semi-automatic segmentation method is feasible in routine clinical practice by observers with a variable level of expertise. Intra-observer agreement is good. Interobserver variability, however, is moderate leading to a relative difference up to 17.9% of the total orbital fat volume. This interobserver variability is higher compared with earlier reports on CT-based analysis¹². This could be explained by the definition of the tissue-specific grey values at the start of the segmentation process. On the CT scan, Hounsfield units (HUs) are universally used to define the tissue. These HUs will stay the same in all circumstances. With the MRI-based analysis, however, the observer has to define a tissue-specific grey value for every patient and in every scan. For this reason, a standard MRI protocol could be more prone to interobserver differences. A strong positive correlation has been shown between fat volume measurements on MRI and CT scan. A tendency for underestimation of fat volume in MRI is observed, which corresponds with findings by Schmutz et al. who compared the orbital volume on CT and MRI¹⁴. The mean difference (1.3 cm³) in fat volume between MRI and CT is in agreement with earlier reports comparing the intact orbital

Fig. 3. Scatterplot and correlation for orbital fat volumetry on magnetic resonance imaging (MRI) and computed tomography (CT) scan. Pearson correlation (r) and P -value are provided.

cavity volume on CT and MRI (differences of up to 1.5 cm^3), although the orbital cavity is probably easier to delineate than the fat tissue^{14,24}. A volume difference greater than 1 cm^3 can be con-

sidered clinically relevant as studies on orbital fat decompression report an average globe displacement of 1 mm for approximately 1 cm^3 fat resection^{25,26}. Conversely, patients diagnosed with GO

are reported to have an increase in orbital fat volume of $4.2\text{--}6.6 \text{ cm}^3$, which could be reliably detected by fat volumetry^{27,7}. Therefore, the measurement error should be taken into account for the purpose of volumetric analysis.

Inflammatory diseases of the orbital fat could have repercussions for imaging outcome, e.g., changing tissue intensities caused by oedema or fibrosis. The success of the automatic segmentation process largely depends on differences in tissue intensities, hence it could be influenced by orbital diseases. When considering the possible influence of orbital tissue deformation or inflammatory disease on volume measurement, results show no significant difference in measurement error for volume calculations in the control group compared with orbits affected by Graves' disease. As this limits the causal role of orbital diseases, other reasons for measurement inaccuracies could be related to the MRI protocol or segmentation method. The accuracy of volumetric measurement depends on an optimal protocol for the correct identification of intensity difference between the region of interest and its surrounding tissues¹⁶. Many MRI orbital protocols have been introduced for the volumetric measurement of orbital tissues. Most studies estimate the orbital fat volume by a manual segmentation technique^{1,2,29,30}. In this approach, the regions of interest have to be defined on every single slice, making it very time

Fig. 4. Bland-Altman plot showing the mean difference (straight line) and 95% limits of agreement (dotted line) between orbital fat volume measurement on computed tomography (CT) and magnetic resonance imaging (MRI).

demanding and impractical³¹. Due to the irregular morphology of the orbital fat, this method is associated with high inter-observer variability and is prone to bias according to the plane orientation of the scan¹⁶. Other studies address this problem by segmenting all but the orbital fat tissue (EOM, globe and optic nerve) and subtract these structures (which are easier to trace) from the whole orbital volume^{2,15,32}. The resulting volume, however, will also contain other tissues such as the lacrimal gland, vessels and connective tissue, which are difficult to distinguish from the fat, causing an overestimation of the true fat volume. More advanced methods such as regional growing and multi-dimensional threshold algorithms try to overcome these problems through a semi-automatic segmentation process but require more dedicated MRI protocols^{9,16,31}. A standard MRI protocol was selected for this study to facilitate availability and make retrospective analysis more feasible. The T1 weighted sequence ensures good contrast between fat and surrounding tissues and is considered first choice in standard orbital imaging. Images were acquired with a slice thickness of 3 mm, which is in line with universally accepted standards reported in literature^{1,2,33,34}. The non-contrast-enhanced sequence allows qualitative and quantitative analysis, avoiding toxicity and cost of gadolinium^{35,36}. More advanced sequences and dedicated acquisition protocols could probably allow for more detailed analysis and enhance the post-processing possibilities^{7,9,16}. It is important to point out, however, that although this could increase opportunities in research setting, these protocols can be highly demanding (staff, scan duration, availability, etc.), which makes everyday use infeasible^{7,31}. Future research can clarify how a standard MRI protocol can be optimized (slice thickness, isotropic voxel, distance factor, etc.) for easier depiction of orbital fat, lower the measurement error and still be efficient for routine use.

To our knowledge, this is the first study to compare a semi-automatic orbital fat volume measurement on MRI and CT. Both imaging studies have specific advantages and can complement each other in the multi-modal management of orbital diseases. This report illustrates the pitfalls and shows to which degree the fat volumetry results can be matched. These insights may contribute to the increasing interest regarding the role of orbital fat tissue in the management of GO but could also give understanding to post-traumatic orbital

changes. This study only includes fat volume analysis, while no correlations were performed with disease activity or severity. This issue has already been extensively discussed by others and goes beyond the focus of this study^{7,9,30}. Considering the relatively small dataset, further studies will be required before these findings can be generalized. MRI measurements were compared with a CT-based method, which was previously validated and considered the clinical reference standard¹². It should be recognized, however, that this method also contains some error compared to the actual anatomical volumes. In future research, authors plan to optimize the MRI protocol, using anatomical specimens to compare with true tissue volume.

In conclusion, this study illustrates the possibilities and the pitfalls of using a standard MRI protocol and a semi-automatic post-processing technique to measure the orbital fat volume. There is a good correlation with CT-based measurements, but the possible error should be considered. Moreover, the inter-observer variability must be improved to allow for implementation as an objective outcome indicator. Enhancing the imaging protocol, with sharper delineation of tissue intensities, is believed to improve the accuracy and inter-observer agreement of MRI segmentation. Future research should focus on tissue-specific MRI acquisition and post-processing techniques, keeping in mind that routine clinical use should be feasible.

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Competing interests

There are no competing interests to disclose.

Ethical approval

The study adhered to the tenets of the declaration of Helsinki. Institutional review board approval and informed consents were obtained (B670201733474).

Patient consent

Not required.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version,

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