Egyptian Journal of Radiology and Nuclear Medicine

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Role of diffusion tensor imaging of extra ocular muscles and orbital fat in Graves's ophthalmopathy and relation to disease activity

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Abstract

Background Graves' ophthalmopathy (GO) is one of the most common autoimmune inflammatory disorders affecting the orbit that characterized by swelling of extra ocular muscles (EOMs) and expansion of the orbital fat. Diffusion tensor imaging (DTI) could assess the microstructural integrity of tissue. We aimed at this study to assess the role of DTI in the evaluation of EOMs and orbital fat in GO and identify the relationship with disease activity.

Results Case–control study included 40 patients diagnosed as Graves' disease (20 active and 20 inactive) and 10 health control subjects underwent DTI. Low fraction anisotropy (FA) and high mean diffusivity (MD) of inferior rectus (IR), medial rectus (MR) and orbital fat in GO versus healthy control (HC), while high FA and high MD in active group versus inactive group. In order to differentiate between GO and HC; FA cutoff point of IR, MR& orbital fat were 0.46, 0.45 and 0.26 with sensitivity 98.8%,98.8% and 93.8% and specificity 95.0%, 95.0% and 85%, respectively. MD cutoff point for IR, MR and orbital fat 1.24, 1.27 and 1.275 with sensitivity 97.5%, 98.8% and 98.8% and specificity 95.0%, 95% and 95%, respectively. To differentiate between active and inactive GO; FA cutoff point of IR, MR and orbital fat were 0.35, 0.36 and 0.22 respectively with sensitivity 80.0%, 82.5% and 72.5% and specificity 95.0%, 85.0% and 65.0%, respectively. MD cutoff point for IR, MR and orbital fat were 1.58, 1.63 and 1.54 respectively with sensitivity 90.0%, 97.5% and 85.0%, and specificity 90.0%, 80.0% and 62.5%, respectively.

Conclusions DTI parameters (FA and MD) of EOMs and orbital fat are considered as crucial radiological biomarkers for diagnosis of GO and could quantitatively differentiate active form inactive disease.

Keywords DTI, FA, MD, EOMs, Graves's ophthalmopathy, Disease activity

Background

Thyroid-associated orbitopathy (TAO), also known as Graves' ophthalmopathy (GO), is one of the most common autoimmune inflammatory disorders affecting the orbit. Autoantibodies against thyroid-stimulating hormone (TSH) receptors in orbital soft tissue is the main immunopathogenesis for GO. Swelling of extra ocular muscles (EOMs) and expansion of the orbital fat are the most conspicuous findings account for clinical presentation of the patients as various clinical symptoms, such as proptosis, dry eye, diplopia and restricted eye movement [1, 2].

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Graves' ophthalmopathy is presented clinically by two phases that has different management: the active phase where mononuclear cell infiltration, edema, and fibroblast proliferation predominate histologically, it lasts for 6–18 months and has potential response to anti-inflammatory treatment. The other phase is the inactive phase that is characterized histologically by interstitial fibrosis with collagen deposition and fat infiltration, patients usually submitted for surgical treatment in this phase [3, 4].

Clinical activity score (CAS) was recommended by the European Group on Graves' Orbitopathy (EUGOGO) consensus as an accurate method for the evaluation of GO activity and assessment of treatment response. Score is calculated by adding 1 point for each of the following symptoms or signs: orbital pain on pressure, orbital pain on movement, swelling, redness of eye lids, conjunctival injection, chemosis and inflammation of the caruncle or plica. When CASexceeds 3, immunosuppressive therapy is recommended. However, CAS doesn't allow appropriate evaluation of various levels of inflammation as the score is unchanged with any improvement or exacerbation until it completely resolves. Low sensitivity besides subjectivity secondary to operator dependency makes the CAS likely impracticable. Thus, there is growing interest in finding appropriate quantitative markers or more reliable imaging features for further CAS validation [5, 6].

Over decades, imaging is standing side by side to the ophthalmological examination and laboratory studies in diagnosis and treatment monitoring of GO patients. MRI is the upper hand imaging tool for GO evaluation owing to its high soft tissue resolution without exposure to ionizing radiation. MRI could provide morphometric assessment of the EOMs besides to T2 signal intensity and contrast enhanced changes that improve diagnostic accuracy of GO and help in disease staging, treatment planning and monitoring [7, 8].

Recently, studies has demonstrated the promising role of diffusion weighted imaging (DWI) in the evaluation of GO. It shows higher ADC in EOMs and lacrimal gland (LG) in disease group compared with control group [9, 10].

Diffusion tensor imaging (DTI) is an emerging technique as advanced tool of the DWI; it could assess the microstructural integrity of tissue quantitatively. Its role in GO evaluation has been aroused in literature in last few years. Few studies have assessed the fraction anisotropy (FA) and diffusivity in EOM, LG and optic nerve (ON) and correlation with disease activity [11–13].

Despite the agreement between several studies that TSH receptors responsible for the immune mechanism of the GO are overexpressed in orbital adipose tissue [14]. To our knowledge, no studies have yet investigated the role of DTI in evaluation of the microstructural integrity of the orbital fat on GO. Therefore, our study aimed to assess the role of DTI in the evaluation of orbital fat besides to EOMs in GO patients and asses the relation with disease activity as well.

Methods

Patients

The Institutional Ethics Committee approved the protocol of the study and informed consent was given by all participants; (IRB code number MD.19.11.247 and date: 4-11-2019). This prospective case–control study included 40 patients diagnosed clinically as Graves' disease and 10 health control (HC) subjects without any thyroid abnormality. Both patients and HCs were recruited from outpatient endocrinology clinic over a period of 20 months from November 2019 to August 2021.

The inclusion criteria included patients with Graves' disease with or without clinically apparent ophthalmopathy based on typical hyperthyroid symptoms (tachycardia, body weight loss, tremor, sweating), a diffuse goiter and positive thyroid-stimulating hormone receptor antibody (TRAb). The control group consisted of age- and sex-matched healthy volunteers with negative results of any thyroid abnormality.

The exclusion criteria were presence of other ophthalmological disease such as glaucoma, history of any chronic illness such as diabetes and hypertension, history of previous exposure to radiation and radioactive iodine, history of previous eye surgery and history of prior immune therapy such as corticosteroid in the previous 6 months to avoid possible effect on CAS scoring, laboratory or DTI data. Also patients with contraindication to MRI, e.g., pacemaker, aneurysmal clips, intraocular foreign body, cochlear implants and claustrophobia are excluded.

Thyroid-stimulating hormone receptor antibody (TRAb) was measured, for both patients and HCs, using third-generation thyroid binding inhibiting immunoglobulin (TBII) with enzyme-linked immunosorbent assay (ELISA) method supplied by Bioassay technology china.

Patients were classified into group I active GO and group II inactive GO based on CAS that was calculated by one endocrinologist having 10 years' experience. A score of three or more on CAS is classified as active GO. Then patients were submitted for MRI examination with time interval between clinical assessment and MRI study was 3–7 days.

Diffusion tensor imaging

First, all subjects and HCs group had underwent conventional MR protocol of the orbit was done using a 1.5-T machine (Ingenia, Philips. Netherland) using dStream Head and Neck 20 channel coil. Routine axial T1WIs

(TR/TE = 620/20 ms), axial and coronal T2WIs (TR/TE = 5430/95 ms) were obtained using matrix of 80 × 80, field of view of 230 × 177 mm^2, and slice thickness of 5 mm were obtained. Then subjects were exposed to diffusion tensor imaging (DTI). DTI data were obtained using a single shot echo planar imaging sequence in coronal plane (TR/TE = 3118/93 ms). The scanning parameters were field of view of 230 × 177 mm^2, data matrix of 92 × 88, and voxel dimensions of 2.43 × 2.54 × 2.5 mm^3. Parallel imaging sensitivity encoding (SENSE) reduction factor P 2 was used. Diffusion gradients were applied along 32 axes, using a b value of 0 and 1000 s/mm^2. Thin section forty-eight slices were obtained, with a thickness of 2.5 mm, no gap, and total scan duration of about 7–8 min.

Image analysis and interpretation

Processing of DTI data was carried out by dedicated work station (Philips Extended MR Workspace 2.6.3.2 with DTI functional tool software). Analysis was done by an expert radiologist in head and neck imaging, 10 years' experience who was blinded to patients' laboratory and clinical data. At first, axial, coronal T1WIs and T2WIs were scanned to assess the extra ocular muscle thickness, signal intensity and to exclude any other abnormality. FA and ADC color maps were extracted. Coronal and axial T2WIs images were applied directly to the opposing co-registered FA and ADC maps in order to accurately measure FA and ADC. Regions of interest (ROI single-pixel seed) were placed in the MR, IR, and retro bulbar fat at both sides (Fig. 1). The calculated muscle thickness, ADC and FA of EOMs besides to mean FA and ADC of the retro bulbar fat were calculated for each orbit and were used for the statistical analysis.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) and mean, standard deviation for parametric data after testing normality using Kolmogorov-Smirnov test. Significance of the obtained results was judged at the (0.05) level.

Results

A case–control study was carried out on 40 patients with Graves' disease that were further subdivided into 20 patients with active Graves orbitopathy (group I), another 20 patients with inactive Graves' orbitopathy (group II) and 10 normal subjects (group III). Group I included 10 males and 10 females, group II included 5 males, 15 females. While, group III included 5 males and 5 females. Their mean ages were 35.50 ± 13.65, 35.80 ± 10.22 and 31.90 ± 9.61 years, respectively.

Activity was determined based on clinical symptoms and laboratory data. Bilateral proptosis was detected in 18 (90%) patients of group I patients versus 2 (10%) patients had unilateral proptosis. Median CAS in group I was 4. Statistical significant difference (P value < 0.001) in thyroid profile laboratory tests was identified between study groups; TSH, FT4 and FT3 in group I were 0.01 (0.0–0.09) mIU/L, 3.69 ± 1.62 and 5.79 ± 0.88 ng/dL, in group II were 0.015 (0.0–0.1) mIU/L, 2.19 ± 0.59 and 4.37 ± 1.11 ng/dL, while in group III were 1.5(0.6–3.0) mIU/L, 1.27 ± 0.18 and 2.60 ± 0.46 ng/dL, respectively. TRAb was 95.6 (65–445), 73.45 (6.7–251.6) and 34.5 (23.8–47.4) IU/L in group I, II and III respectively with

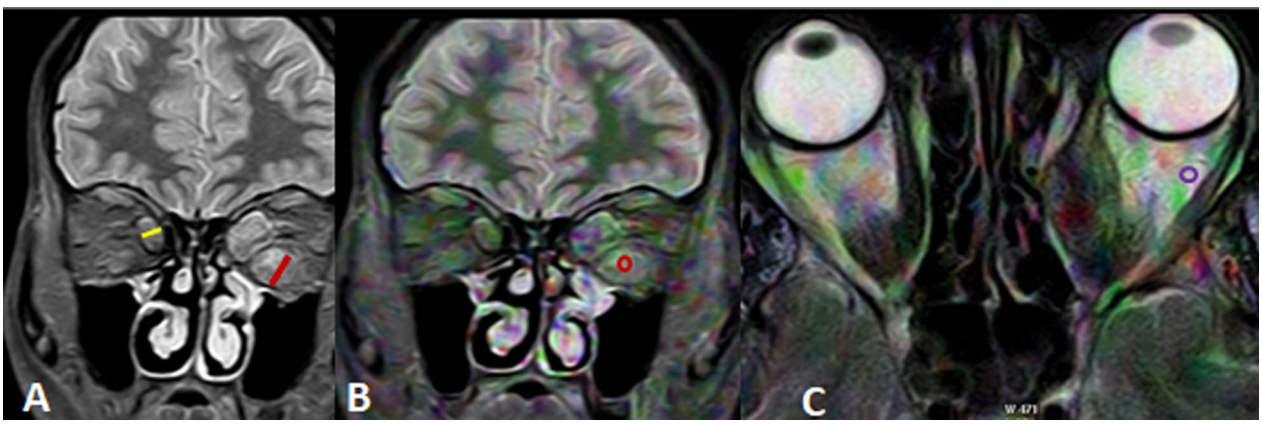

Fig. 1 A 57-year-old male patient has active Graves' disease, complaining of bilateral proptosis, CAS score was 6. **A** Coronal STIR image of both orbits (yellow and red lines) refers to thickness measurement of MR and IR = 6.4 mm and 8.8 mm, respectively. **B** Coronal co-registered DTI (red circle) refers to ROI for measurement of MD and FA of IR = 1.8 and 0.41, respectively. **C** Axial co-registered DTI (purple circle) refers to ROI for measurement of orbital fat MD and FA = 1.58 and 0.25, respectively

statistically significant (P value < 0.001) high sensitivity (98.8%) and specificity (90%) in differentiation between patients with Graves' disease and health control. Whilst, it showed statistically significant difference (P value < 0.005) in differentiation between active and inactive GO with sensitivity (80.0%) and specificity (45.0%).

IR and MR thickness was statistically higher (P value < 0.001) in GO patients than control subjects, while only IR muscle thickness was significantly higher in active group compared to inactive group (P value < 0.048). Statistically significant (P value < 0.001) low FA and high MD of both IR, MR as well as orbital fat was identified in GO patients versus control subjects, while high FA and high MD in active group versus inactive group as shown in (Tables 1, 2) and (Figs. 2, 3).

FA cutoff points of IR and MR and orbital fat to differentiate between GO and health control were 0.46, 0.**45** and 0.2**6** with high sensitivity and specificity. Meanwhile MD cutoff point for IR, MR and orbital fat to differentiate between GO and health control were 1.24, 1.27 and 1.275×10^{-3} mm^2/s respectively with very high sensitivity and specificity, as shown in (Table 3). Orbital fat MD had higher specificity (95%) than FA (85%) with comparable high sensitivity in differentiation between GO patients and health control subjects (Fig. 4).

Concerning differentiation between active and inactive groups, Table 3 has shown FA cutoff point of IR, MR and orbital fat were 0.35, 0.36 and 0.22, respectively. MD cutoff point for IR, MR and orbital fat were 1.58, 1.63 and 1.54×10^{-3} mm^2/s respectively with highest specificity for IR FA and highest sensitivity for MR MD, while orbital fat MD had higher sensitivity than FA with comparable lower specificity (Fig. 5).

Regarding the correlation between DTI parameters of EOM, orbital fat & clinical and laboratory biomarkers, there was a statistically significant negative correlation between CAS and IR FA($r = -0.354$, p value = 0.025) and positive correlation with IR MD ($r = 0.360$, p value = 0.023). Meanwhile, a statistically significant positive correlation was detected between TRAb and the following; IR MD ($r = 0.481$, p value = 0.001), MR MD($r = 0.479$, p value = 0.001) and Fat MD ($r = 0.300$, p value = 0.007).

Table 1 IR, MR fat thickness, FA& MD between cases and control

	Diseased patients	Control group	Test of significance
IR thick	4.62 ± 1.44	2.66 ± 0.45	$t = 5.97$ $p < 0.001$*
MR thick	4.39 ± 1.56	2.62 ± 0.44	$t = 5.03$ $p < 0.001$*
FA			
IR	0.364 ± 0.048	0.538 ± 0.041	$t = 14.83$ $p < 0.001$*
MR	0.362 ± 0.051	0.514 ± 0.039	$t = 12.51$ $p < 0.001$*
FAT	0.220 ± 0.272	0.298 ± 0.032	$t = 10.73$ $p < 0.001$*
MD			
IR	1.60 ± 0.17	1.09 ± 0.13	$t = 12.61$ $p < 0.001$*
MR	1.62 ± 0.19	1.14 ± 0.11	$t = 10.82$ $p < 0.001$*
FAT	1.519 ± 0.165	1.129 ± 0.114	$t = 10.01$ $p < 0.001$*

IR, inferior rectus; MR, medial rectus; FA, fraction anisotropy; MD, mean diffusivity; t, student t test parameters described as mean ± SD, *statistically significant

Table 2 IR, MR, fat thickness, FA&MD between active and inactive groups

	Active group	Inactive group	*P* value
IR thick	4.91 ± 1.63	4.33 ± 1.18	0.048*
MR thick	4.66 ± 1.91	4.14 ± 1.07	0.09
FA			
IR	0.398 ± 0.029	0.330 ± 0.03 8	< 0.001*
MR	0.395 ± 0.031	0.330 ± 0.045	< 0.001*
FAT	0.231 ± 0.02	0.213 ± 0.029	0.004*
MD			
IR	1.73 ± 0.13	1.47 ± 0.09	< 0.001*
MR	1.76 ± 0.16	1.48 ± 0.09	< 0.001*
FAT	1.59 ± 0.18	1.44 ± 0.098	< 0.001*

IR, inferior rectus; MR, medial rectus; FA, fraction anisotropy; MD, Mean diffusivity. *Statistically significant

Discussion

Extra ocular muscle consists of wellarranged and integrated muscle fibers and display anisotropy, hence, its microstructural integrity and strength can be investigated by diffusion tensor imaging providing objective findings to improve diagnostic accuracy [15]. Orbital fat is a primary target of immune attack in GO and responsible for clinical symptomatology of patients as proptosis secondary to both adipogenesis and inflammatory reaction [16].

Therefore, our study aimed to investigate the role of DTI in the evaluation of orbital fat besides to EOMs in GO patients and asses the relation with disease activity as well.

In the present study, coronal plane was used instead to axial images to simultaneously measure the thickness of MR and IR; the two commonly affected muscles in GO in order to save time. Muscle thickness of MR and IR was higher in GO than HC, this came in agreement with Parmar et al. [17] and Karhanová et al. [18] who described MR as the most frequently affected muscle in cases with

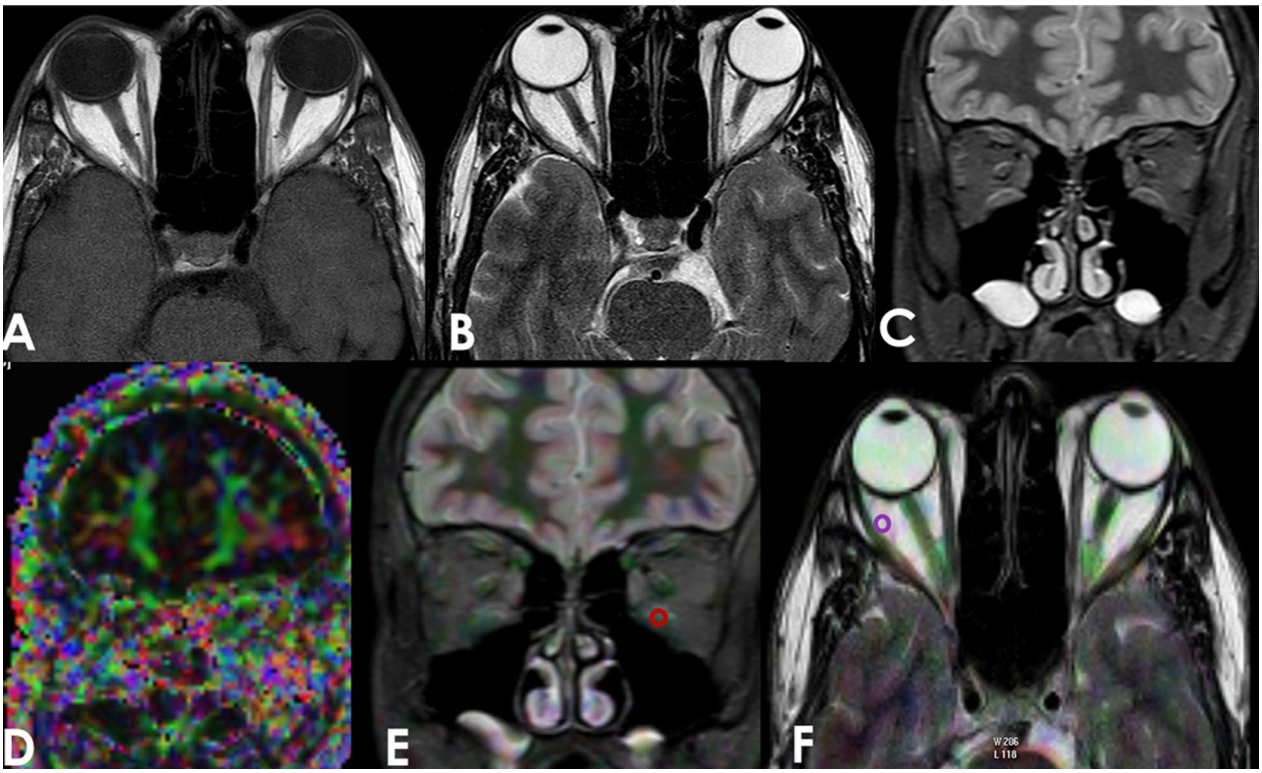

Fig. 2 An 18-year-old male patient, active Graves' disease, complaining of bilateral proptosis, CAS score was 6. **A**–**C** Axial T1WI, axial T2WI and coronal STIR image of both orbits muscle thickness of MR and IR = 5.8 mm and 4.9 mm, respectively. **D** Coronal FA color map for qualitative display of FA values of EOMs. **E** Coronal co-registered DTI (red circle) refers to ROI for measurement of MD and FA of IR = 1.68 and 0.41, respectively. **F** Axial co-registered DTI (purple circle) refers to ROI for measurement of orbital fat MD and FA = 1.62 and 0.25, respectively

multiple muscle enlargement. While only IR muscle was significantly thicker in active group compared to inactive group, this came in accordance with study done by Xu et al. [19] in which IR was thicker in moderate to server GO, and its ratio to orbital fat was used to predict responsiveness to glucocorticoid therapy.

Considering the role of DTI in EOMs and orbital fat in GO, our study showed low FA and high MD values of both IR and MR muscles and orbital fat in GO compared to HC. This is likely attributed to histopathological changes occurs in GO. Bahn [20] described edema, lymphocytic infiltration, and fibrosis in muscles and adipose tissue in GO on microscopy with subsequent increased volume. Edema is explained by hydrophilic effect of collagen and glycosaminoglycans (GAGs) that are deposited throughout the muscle fibers in the endomysial space and retro ocular tissue [17]. This may result in increased diffusivity of water molecules within the tissue where its magnitude is measured by MD. Meanwhile, FA reflects degree of anisotropy related to tissue architecture and fiber integrity [21]; therefore, it was not surprising that FA will decrease in EOM and fat secondary to microstructural changes in GO patients.

This is keeping with prior recent studies Chen et al. [22, 23] and Rui et al. [24] who described low FA and high MD in EOMs, lacrimal glands, and optic nerve (ON) in GO patients compared to HC. In present study, same parameters alterations were also detected in orbital fat. Both DTI parameters showed high areas under curve with high sensitivity and specificity in differentiation between GO and HC.

For discrimination between active and inactive patients, the current study showed statistically significant higher FA and higher MD for EOMs and fat in active GO compared to inactive group. This also came in agreement with Chen et al. [22, 23]. Edema and mononuclear cell infiltration is the histopathological hallmark of active phase with subsequent more increase in tissue diffusivity and higher MD. Meanwhile, the hallmark of the inactive chronic phase is collagen deposition, fibrosis and fatty infiltration with further tissue disruption and cell loss. So it was expected that FA will be reduced in inactive group [17].

The present study showed high area under curve of DTI parameters of EOM than orbital fat in differentiation between active and inactive groups. Cutoff point 0.35 for

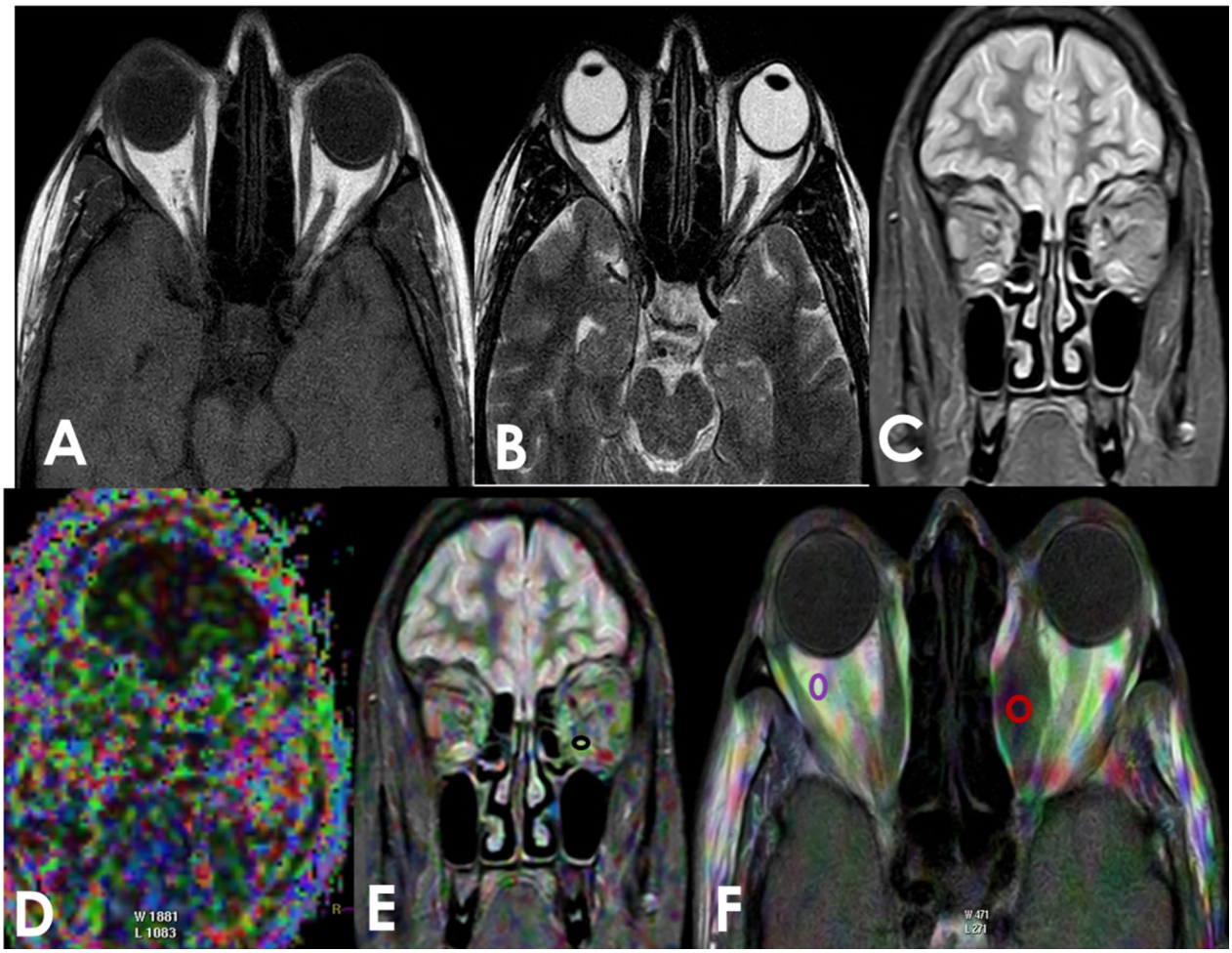

Fig. 3 A 48-year-old female patient, inactive Graves' disease complaining of bilateral proptosis, CAS score was 0. **A**–**C** Axial T1WI, axial T2WI and coronal STIR image of both orbits muscle thickness of MR and IR = 5.5 mm and 5.7 mm, respectively. **D** Coronal FA color map for qualitative display of FA values of EOMs. **E** Coronal co-registered DTI (black circle) refers to ROI for measurement of MD and FA of IR = 1.5 and 0.29, respectively. **F** Axial co-registered DTI image (red circle) refers to ROI for measurement of MD and FA of MR = 1.47 and 0.31, respectively, (purple circle) refers to ROI for measurement of orbital fat MD and FA = 1.43 and 0.23, respectively

FA-IR achieves specificity 95.0%, while cutoff point 1.63 for MD-MR achieved sensitivity 97.6%. In contradictory, orbital fat FA cutoff point 0.22 showed low sensitivity and specificity (72.5% and 65.5%), respectively, while fat MD cutoff point showed high sensitivity and low specificity (85% and 62.5%), respectively. This may be related to different cytokine profiles that are integrated in immunologic mechanism of GO between the EOM and fat. So, GO patients could be classified as having predominantly increased orbital fat or predominantly enlarged extra ocular muscles [25, 26], while our study's patients may belong to the latter one.

Understanding the histopathological changes occurring in GO patients, both active and in active groups besides to their reflection on DTI parameters, it was expectedly that CAS will be correlated with these DTI parameters. In the present study, CAS was negatively correlated with FA-IR and positively correlated with MD-IR. This keeps with Rui et al. [24] who suggested that DTI parameters of EOM are sensitive imaging indicators, which could distinguish mild from moderate-severe TAO patients and can be used as radiological indicators for decision-making.

In the current study, TRAb was significantly higher in GO patients than HC and in active group compared to the inactive group. It was described in previous studies that TSH receptor are over expressed by orbital tissue fibroblasts in thyroid eye disease. Their circulating autoantibodies are acting through these receptors and stimulate a cascade of changes resulting eventually in

Table 3 Validity of FA and MD of IR, MR& FAT in differentiating between studied groups

	AUC (95% CI)	*P* Value	Cut off point	Sensitivity%	Specificity%
Between active and inactive groups					
FA					
IR	909 (0.842–0.976)	< 0.001*	0.355	80.0	95.0
MR	874 (0.793–0.955)	< 0.001*	0.365	82.5	85.0
FAT	0.727 (0.615–0.838)	< 0.001*	0.225	72.5	65.0
MD					
IR	0.951 (0.904–0.999)	< 0.001*	1.585	90.0	90.0
MR	0.942 (0892–0.991)	< 0.001*	1.635	97.5	80.0
Fat	0.777 (0.675–0.879)	< 0.001*	1.54	85.0	62.5
Between diseased patients & control group					
FA					
IR	0.998(0.993–1.0)	< 0.001*	0.465	98.8	95.0
MR	0.997(0.989–1.0)	< 0.001*	0.460	98.8	95.0
FAT	0.957(0.908–1.0)	< 0.001*	0.265	93.8	85.0
MD					
IR	0.993 (0.982–1.0)	< 0.001*	1.24	97.5	95.0
MR	0.994 (0.983–1.0)	< 0.001*	1.27	98.8	95.0
FAT	0.997 (0.991–1.0)	< 0.001*	1.275	98.8	95.0

IR, inferior rectus; MR, medial rectus; FA, fraction anisotropy; MD, mean diffusivity

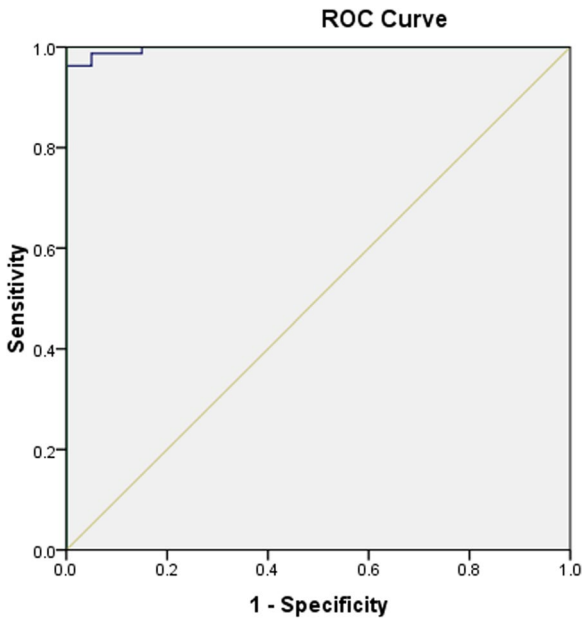

Fig. 4 ROC curve for fat MD by MRI in differentiating between diseased patients and control group

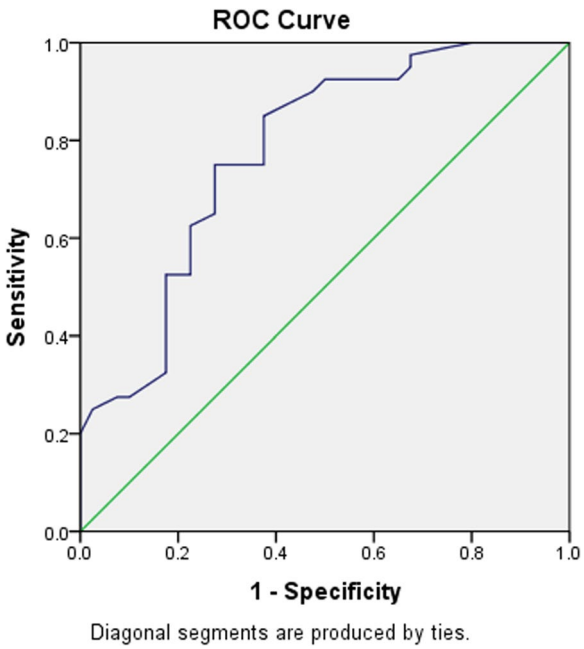

Fig. 5 ROC curve for orbital Fat MD by MRI in differentiating between group active and inactive groups

tissue edema and expansion thus TRAb played a key role not only in diagnosis of thyroid eye disease but also as indicative and predictive of disease activity [27, 28]. So, it was unsurprisingly that TRAb correlated positively with MD (biomarker of tissue edema) of EOMs and orbital fat.

Our study had some limitations; first of all was small number of included patients aiming to increase sample size in the future. Secondly, mean diffusivity was only measured in this study, meanwhile radial (RD) and axial diffusivity (AD) are advised for further assessment. Thirdly, lack of correlation between the DTI parameters of orbital fat with EOMs and lack of follow-up of patients after treatment, thus optimization of the DTI technique and including patients after treatment are recommended for future studies for comprehensive understanding of GO. Lastly, there was a single interpreting radiologist, thus adding another observer in future and assessing inter observer reliability may be beneficial.

Conclusion

DTI parameters including FA and MD of EOMs and orbital fat are crucial radiological biomarkers for diagnosis of GO, could quantitatively differentiate active form inactive disease& and can be added to activity indicators of disease.

Abbreviations

CAS	Clinical activity score
DTI	Diffusion tensor imaging
FA	Fraction anisotropy
GO	Graves' ophthalmopathy
HC	Healthy control
IR	Inferior rectus
MD	Mean diffusivity
MR	Medial rectus
TAO	Thyroid-associated orbitopathy
TRAb	Thyroid-stimulating hormone receptor antibody

Acknowledgements

Not applicable.

Author contributions

MGH, MR, AAKH designed the research. MM performed the research and wrote the manuscript. MM, AB, MR analyzed the collected data. MGH, AM, AB revised data and manuscript. All authors read and approved the final manuscript.

Funding

Not applicable (no funding received for this study).

Availability of data and materials

Available on request with the corresponding author.

Declarations

Ethics approval and consent to participate

This study was approved by the research ethics committee of Mansoura Faculty of Medicine. Mansoura University on 04/11/2019, Reference number of approval: MD.19.11.247.

Informed consent

All patients included in this study gave a written informed consent to participate in the research.

Consent for publication

All patients included in this study gave a written informed consent to publish the data contained in this study.

Competing interests

The authors declare that they have no competing interests.

Received: 3 April 2024 Accepted: 26 July 2024
Published online: 07 August 2024

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