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Application of apparent diffusion coefficient of extraocular muscles from diffusion tensor imaging scanning in the assessment of disease activity of thyroid eye disease

Cheng Yang Tang¹, Qian Huang¹, Liang Liang², Ming Qiao Zhang¹, Xiao Ya Zheng¹ and Jian Long^{1*} 

Abstract

Purpose To evaluate the utility of apparent diffusion coefficient (ADC) values of extraocular muscles (EOMs) in differentiating activity of thyroid eye disease (TED).

Method Forty-two TED patients who underwent diffusion tensor imaging (DTI) were retrospectively enrolled in this study, including 29 patients in analysis group and 13 patients in validation group. The mean, maximum and minimum ADC value of each EOM were regarded as ADC_{mean}, ADC_{max} and ADC_{min}. The difference between ADC_{max} and ADC_{min} was regarded as Δ ADC. The correlations between ADC_{mean} or Δ ADC of each EOM and clinical activity score (CAS) were assessed.

Results In analysis group, ADC_{mean} differed between active and inactive eyes and positively correlated with CAS in IR ($P < 0.05$), not in SR, LR and MR (all $p > 0.05$). While Δ ADC differed between two groups and negatively correlated with CAS in all EOMs (all $P < 0.05$). ADC_{mean} predicted active disease at cut-off value of $1259.3 \times 10^{-6} \text{mm}^2 \text{s}^{-1}$ with sensitivity of 66.7% and specificity of 71.4% in IR [area under curve = 0.667, $P < 0.05$]. Δ ADC predicted disease activity in all EOMs [area under curve 0.658–0.746, all $P < 0.05$]. The cut-off values of Δ ADC were 382, 823, 520 and $572 \times 10^{-6} \text{mm}^2 \text{s}^{-1}$ with sensitivity of 80.0%, 50.0%, 43.3%, 83.3% and specificity of 67.9%, 85.7%, 89.3%, 60.7% in SR, IR, MR, and LR respectively. There were no significant differences in the predictive efficacy among all cut-off values.

Conclusions Our results showed that DTI is a valuable tool in the assessment of disease activity of TED. Both ADC_{mean} of IR and Δ ADC of all four EOMs can be used in discriminating disease activity with the same predictive power.

Keywords Thyroid eye disease, CAS, ADC, Resolve DTI, EOMs

Introduction

Thyroid eye disease (TED) is one of the most common orbital inflammatory diseases with the clinical manifestations including eyelid retraction, lid lag, proptosis, extraocular muscle restriction, exposure keratopathy, and optic neuropathy [1–3]. The whole pathological process is divided into two stages: active stage and inactive stage [4]. The active stage is characterized by infiltration and edema of inflammatory cells in the orbit. While the inactive stage is featured with fibrosis and the hyperplasia

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of extraocular muscles (EOMs) and fat. Patients in active stage respond well to immunosuppressive treatment. While patients in inactive stage can not benefit from that [3, 5]. Therefore, the accurate assessment of disease activity is critical to treatment selection.

Currently, the assessment of disease activity is mainly based on the Clinical activity Score (CAS), which is the sum of 7 or 10 clinical items [6]. The higher the CAS score, the higher the activity. However, CAS is not without its limitations. Firstly, the score is mainly based on the clinical evaluation of the ocular surface rather than the inflammation deep in the orbit [1, 7]. Secondly CAS is a subjective parameter with poor consistency. Thus, it is necessary to find objective and reliable indicators of disease activity.

DTI is a noninvasive and advanced MRI technique, which can visualize water motion at the molecular level in three-dimensional space and provide information of directed diffusion of water [8–10]. Resolve DTI can improve quality of image and perform well in distinguishing normal anatomical structures [11]. The apparent diffusion coefficient (ADC) is a quantitative parameter of DTI, and its value increases with the increase of inflammation, edema, or tissue fluid [12–15]. In TED, previous studies have showed that ADC values of lacrimal gland was significantly higher in active patients than in inactive patients [16, 17]. This suggested that ADC may reflect inflammatory activity in TED. While, it is well known that EOMs are the main lesion sites in TED, not lacrimal gland [18, 19]. We speculated that ADC values of EOMs may be a good predictor for disease activity of TED. However, no published data was found.

Therefore, we performed orbital MRI scans with Resolve DTI sequence in TED patients to evaluate the diagnostic value of ADC values of EOMs for disease activity.

Methods

Population

From January 2020 to December 2021, TED patients who visited the First Affiliated Hospital of Chongqing Medical University were recruited. The inclusion criteria were as follows: (1) age of >18 years and <75 years; (2) TED patients who had undergone orbital MRI scans with Resolve DTI sequence. The exclusion criteria were as follows: (1) previous history of glucocorticoid therapy or other immunosuppressant, radiotherapy, or surgical decompression surgery; (2) other causes of orbital disease such as tumor, trauma or other immunological disorders such as Multiple sclerosis, Systemic Lupus Erythematosus et al.; (3) image quality was inadequate for further analysis. All subjects agreed to take part in the present study and signed the consent form. The study followed the

tenets of the declaration of Helsinki and was approved by the First Affiliated Hospital of Chongqing Medical University Ethical Committee. All methods and designs were performed in accordance with the consensus statement of the European Group on Graves' Orbitopathy criteria.

Clinical and biochemical measurements

External and funduscopic exam, visual acuity, intraocular pressure (IOP) (noncontact tonometer CT-1, Topcon, Japan) and exophthalmometry (66vision Technology Co, Ltd, Suzhou, China) were evaluated by an ophthalmologist in all patients. The diagnosis and evaluation of TED followed the consensus statement of the European Group on Graves' eye (EUGOGO) criteria [6]. The CAS consists of seven findings: spontaneous retrobulbar pain; pain on attempted up or down gaze; redness of the conjunctiva; redness of the eyelids; inflammation of the caruncle and/or plica; swelling of the eyelids; and conjunctival edema. Each finding was scored 1 point. A summed CAS score of ≥ 3 was considered as active TED.

Image acquisition

MRI scan was performed in all patients using a 3.0-T MRI system (Skyra, Siemens, Germany) with a 20-channel head coil. Patients were asked to rest in supine position and look at a fixed site with eyes closed in order to reduce motion-related artifacts. Orbital coronal DTI images and conventional images were collected respectively. The ADC values in the superior rectus (SR), inferior rectus (IR), medial rectus (MR) and lateral rectus (LR) were measured on the DTI images which scanned by the routine scan protocol (repetition time (TR) = 4170 ms, echo time (TE) = 70 ms, FOV = 180 mm × 180 mm, slice thickness = 2.5 mm, interval between layers = 0.25 mm, scanning time = 283 s).

Magnetic resonance image (MRI) analysis

Siemens post-processing workstation was used to analyze DTI for measurement. With an MRI scan of the eye, there were 3–5 consecutive sections of each EOM. ROIs were drawn manually on each section of each EOM in areas with obvious inflammation visible to observers. Since it's difficult to distinguish the superior rectus muscle and the levator palpebrae superioris from each other, they were measured together. After ROIs were placed, ADC values of each section were obtained in each eye (Fig. 1). The mean, maximum and minimum ADC values of all sections in each EOM were regarded as ADC_{mean}, ADC_{max} and ADC_{min}. The difference between ADC_{max} and ADC_{min} was regarded as Δ ADC. The measurements were performed by two independent observers. The results of the two observers had excellent inter-reader agreement with an intra-class correlation

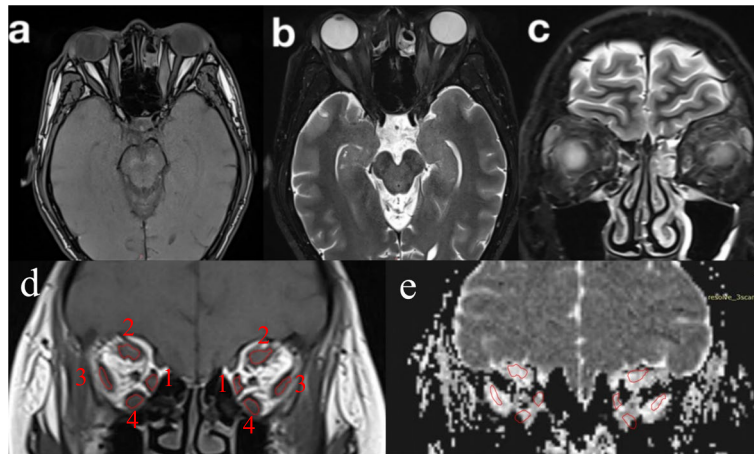


Fig. 1 Orbital MRI of a 58-year-old male with TAO. **a-b** Axial T1- and T2-weighted imaging shows the orbit. **c,d** Coronal T2- and T1-weighted imaging shows the quantitative measurements of the EOMs. **e** ADC map shows the quantitative measurements of the EOMs. The number from 1 to 4 represent medial rectus, superior rectus, lateral rectus and inferior rectus respectively. MRI, magnetic resonance imaging; TAO, thyroid associated ophthalmopathy; EOMs, extraocular muscles; ADC, apparent diffusion coefficient

coefficient (ICC) of 0.98. Then the results of the observer 1 were used for further statistical analysis.

Statistical analysis

SPSS (version 26.0) was used for statistical analysis. All results were reported as the mean \pm standard deviation. The Shapiro–Wilk test was conducted to test the normality of all continuous variables. Means of continuous variable were compared using the Unpaired t-test, or Mann–Whitney Test (when the data were not normally distributed). Pearson correlation test was used to evaluate the correlations between CAS and ADC. The receiver operating characteristic (ROC) curve was done to determine the cut-off point of the ADC value of EOMs used to differentiate TED from active and inactive eyes with calculation of area under the curve (AUC). The sensitivity and specificity were also obtained with further analysis. Statistical analysis regarding the ROC were conducted using the MedCalc software. Differences were statistically significant at $P < 0.05$.

Results

A total of 42 TED patients were enrolled in this study, including 29 patients in analysis group and 13 patients in validation group. In analysis group, the mean age was 47.78 ± 5.15 years. The duration of TED was 19.04 ± 15.49 months. Nine of them were male (31.03%). Five of them were smoker (17.24%).

The clinical characteristics of active and inactive eyes

Fifty-eight eyes of 29 TED patients in analysis group were divided into active ($n=28$) and inactive eyes ($n=30$) based on CAS. As shown in Table 1, compared with inactive eyes, active eyes had much worse eyesight, higher intraocular pressure and degree of exophthalmos.

ADC values of each EOM in active and inactive eyes

As shown in Table 2, ADC mean differed between the two groups in IR ($1289.45 \pm 90.44 \times 10^{-6} \text{mm}^2 \text{s}^{-1}$ vs $1161.18 \pm 88.87 \times 10^{-6} \text{mm}^2 \text{s}^{-1}$; $P=0.029$), not in SR, LR and MR (all $p > 0.05$). Δ ADC differed between the two groups in all four EOMs (

Table 1 The clinical characteristics of active and inactive eyes

	Active eyes ($n=28$)	Inactive eyes ($n=30$)	P-value
Eyesight	0.58 ± 0.14	0.83 ± 0.10	0.010#
Intraocular pressure (mmHg)	20.75 ± 1.89	17.43 ± 0.77	0.002*
Exophthalmos (mm)	20.63 ± 1.07	18.00 ± 0.99	0.001#
CAS	3.82 ± 0.33	1.17 ± 0.14	0.000#

Data represented as mean \pm SD; n number

*: the Unpaired t-test

#: Mann–Whitney Test

P-value < 0.05 was considered to be significant

Table 2 The ADCmean and ΔADC value of each EOM in active and inactive eyes

	Active eyes(n=28)	Inactive eyes(n=30)	P-Value
ADCmean of SR	1412.21 ± 89.56	1508.57 ± 108.62	0.170*
ADCmean of IR	1289.45 ± 90.44	1161.18 ± 88.87	0.029#
ADCmean of MR	1526.72 ± 80.57	1396.41 ± 124.84	0.079*
ADCmean of LR	1297.67 ± 106.56	1256.01 ± 108.15	0.577*
ΔADC of SR	392.18 ± 101.04	555.7 ± 80.23	0.001#
ΔADC of IR	581.46 ± 162.67	880.77 ± 193.43	0.039#
ΔADC of MR	344.32 ± 78.81	476.13 ± 93.04	0.032*
ΔADC of LR	677.39 ± 187.22	1154.97 ± 295.04	0.011#

ADCmean: the average ADC value of five planes, SR Superior rectus, IR Inferior rectus, MR Medial rectus, LR Lateral rectus, n number

Data represented as mean ± SD

*: The Unpaired t-test

#: Mann-Whitney Test

Q- value < 0.05 was considered to be significant

Table 3 The association between ADC values of each EOM and CAS

	r	P-Value
ADCmean of IR	0.27	0.043
ΔADC of SR	-0.33	0.011
ΔADC of IR	-0.31	0.019
ΔADC of MR	-0.28	0.032
ΔADC of LR	-0.35	0.008

EOM extraocular muscle, CAS clinical activity score, SR Superior rectus, IR Inferior rectus, MR Medial rectus, LR Lateral rectus, ΔADC the difference between the maximum and minimum ADC value

Pearson correlation test was used to evaluate the correlations

P-value < 0.05 was considered to be significant

SR: $392.18 \pm 101.04 \times 10^{-6} \text{mm}^2 \text{s}^{-1}$ vs. $555.7 \pm 80.23 \times 10^{-6} \text{mm}^2 \text{s}^{-1}$, $P=0.001$;

IR: $581.46 \pm 162.67 \times 10^{-6} \text{mm}^2 \text{s}^{-1}$ vs. $880.77 \pm 193.43 \times 10^{-6} \text{mm}^2 \text{s}^{-1}$, $P=0.039$;

MR: $344.32 \pm 78.81 \times 10^{-6} \text{mm}^2 \text{s}^{-1}$ vs. $476.13 \pm 93.04 \times 10^{-6} \text{mm}^2 \text{s}^{-1}$, $P=0.032$;

LR: $677.39 \pm 187.22 \times 10^{-6} \text{mm}^2 \text{s}^{-1}$ vs. $1154.97 \pm 295.04 \times 10^{-6} \text{mm}^2 \text{s}^{-1}$, $P=0.011$).

Correlations between ADC values and CAS

As shown in Table 3, ADCmean of IR showed positive correlation with CAS ($P=0.043$, $R=0.27$). ΔADC showed negative correlation with CAS in SR ($P=0.011$, $R=-0.330$), IR ($P=0.019$, $R=-0.306$), MR ($P=0.032$, $R=-0.282$) and LR ($P=0.008$, $R=-0.345$).

Receiver operating characteristic (ROC) cure analysis

To determine the predictive efficiency and diagnostic cut-off value, we performed ROC curve analysis in Table 4. The cut-off value of ADCmean used to predict active disease was $>1259.3 \times 10^{-6} \text{mm}^2 \text{s}^{-1}$ with a sensitivity of 66.7% and a specificity of 71.4% in IR (AUC:0.667, $P=0.029$). ΔADC performed well in discriminating activity in all four EOMs (SR:AUC=0.746, $P=0.001$; IR:AUC=0.675, $P=0.022$; MR:AUC=0.658, $P=0.039$ and LR:AUC=0.695, $P=0.011$). The cut-off value of ΔADC were $>382 \times 10^{-6} \text{mm}^2 \text{s}^{-1}$ in SR, $>823 \times 10^{-6} \text{mm}^2 \text{s}^{-1}$ in IR, $>520 \times 10^{-6} \text{mm}^2 \text{s}^{-1}$ in MR and $>572 \times 10^{-6} \text{mm}^2 \text{s}^{-1}$ in LR. And the sensitivity were 80.0%, 50.0%, 43.3%, 83.3% and the specificity were 67.9%, 85.7%, 89.3%, 60.7% in SR, IR, MR, and LR respectively.

The diagnostic accuracy of the identified cut-off values was further validated in validation group in Table 4 ($n=26$). Twenty-six eyes were classified into active and inactive group according to the identified cut-offs and matched with their actual CAS. The diagnostic sensitivity and specificity for the cut-off of ADCmean of IR was 68.42% and 57.14%. The diagnostic sensitivity and specificity for the cut-off of ΔADC were 68.42%, 63.16%, 68.42%, 68.42% and 71.43%, 57.14%, 57.14%, 85.71% in SR, IR, MR, and LR respectively.

Table 4 Predictive performance of ADC values of each EOM between the active and inactive eyes

	AUC	Cut-off	Sensitivity %	Sensitivity %	P-value	Validation of Cut-offs	
						Sensitivity%	Specificity%
ADCmean of IR	0.667	1259.3	66.70	71.4	0.029	68.42	57.14
ΔADC of SR	0.746	382.00	80.00	67.90	0.001	68.42	71.43
ΔADC of IR	0.675	823.00	50.00	85.70	0.022	63.16	57.14
ΔADC of MR	0.658	520.00	43.30	89.30	0.039	68.42	57.14
ΔADC of LR	0.695	572.00	83.30	60.70	0.011	68.42	85.71

AUC Area under curve, EOM extraocular muscle, ΔADC the difference between the maximum and minimum ADC value, SR Superior rectus, IR Inferior rectus, MR Medial rectus, LR Lateral rectus

P value < 0.05 was considered to be significant

Table 5 The predictive efficacy between different ADC values

	Δ ADC						ADCmean of IR vs Δ ADC of each EOM			
	SR vs IR	SR vs MR	SR vs LR	IR vs MR	IR vs LR	MR vs LR	IR vs SR	IR vs IR	IR vs MR	IR vs LR
P-value	0.416	0.367	0.514	0.840	0.835	0.350	0.374	0.927	0.929	0.794

Δ ADC the difference between the maximum and minimum ADC value, SR Superior rectus, IR Inferior rectus, MR Medial rectus, LR Lateral rectus

Delong's test was used to evaluate the predictive efficacy between different Δ ADC

P-value < 0.05 was considered to be significant

The predictive efficacy between different Δ ADC values

To find the best predictor, the predictive efficacy of different ADC were compared in Table 5. There were no significant differences in the predictive efficacy of Δ ADC cut-off values among SR, IR, MR, LR (all $P > 0.05$). Also there were no significant differences in the predictive efficacy between ADCmean of IR and Δ ADC cut-off values (all $P > 0.05$).

Discussion

Our study demonstrated that Δ ADC of all four EOMs and ADCmean of IR could predict disease activity in TED. This was the first study to show that DTI parameters of a single EOM can be used to assess disease activity of TED.

Previous studies have shown that inflammation can increase ADC values of tissue [12–14, 20, 22]. The active stage of TED is characterized by lymphocytic cell infiltration, edema and inflammation. The inactive stage is characterized by adipogenesis and myofibrillogenesis. During the active stage, the inflammation of EOMs is more severe and even. In active stage, the inflammation is reduced, uneven distribution.

ADCmean is the average ADC value of 3–5 layers of the whole muscle. We found that ADCmean was positively correlated with CAS in IR which was in line with previous studies.

But this relationship was not found in SR, LR and MR. The reason for the difference results was not clear. There may be several explanations for that. Firstly, IR was reported to be the most susceptible muscle among all four EOMs [18, 19, 21]. Secondly, we thought that the inflammations of EOMs might be not uniform in each part, therefore, using ADCmean to represent the entire EOMs may result in some loss of information.

We thought that Δ ADC could reflect the heterogeneity of water diffusion in different parts of EOMs and might better reflect the inflammation of EOMs, which is the difference between ADC maximum and ADC minimum. Therefore, we calculated Δ ADC of each EOM and assessed the correlations between Δ ADC and CAS. As expected, Δ ADC differed between active and inactive

eyes and negatively correlated with CAS in all four EOMs in our study.

To prove our results, we calculated the cut-off value of Δ ADC and ADCmean and validate them in another 26 TED eyes. Our data showed that both Δ ADC of all four EOMs and ADCmean of IR could predict disease activity with good sensitivity and specificity.

To find the best predictor, the predictive effects of Δ ADC and ADCmean were compared. We found the same predictive value for disease activity among Δ ADC values of four EOMs, as well as between Δ ADC and ADCmean. Therefore for clinical applications, both Δ ADC of any EOM or ADCmean of IR can be selected.

The present study had several limitations. First, this was a retrospective study and sample size was relatively small. Second, due to the difficulties in achieving the histological analysis of EOMs, the disease activity was based on the CAS. Therefore, although the identified cut-offs were validated in a new group of patients, the accuracy of the predicting values need to be validated in future large population.

Conclusion

Our results showed that DTI is a valuable tool in the assessment of disease activity of TED. Both ADCmean of IR and Δ ADC of all four EOMs can be used in discriminating disease activity with the same predictive power.

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Authors' contributions

Liang liang contributed to the diagnosis and assessment of TED. Cheng yang Tang and Qian Huang performed parameter measurements. Ming qiao zhang and Cheng yang Tang contributed to data analysis. Cheng yang Tang and Long jian contributed to manuscript preparation. Xiaoya zheng, and Longjian contributed to the conception of the study. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

We confirmed that informed consent was obtained from all subjects, all subjects recruited agreed to take part in the present study. The study was approved by the First Affiliated Hospital of Chongqing Medical University Ethical Committee. All methods and designs were performed in accordance with the consensus statement of the European Group on Graves' Orbitopathy criteria.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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