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Thyroid-Associated Ophthalmopathy with Diplopia: A Magnetic Resonance Imaging–Based Correlational Study of Intraorbital Tissues and Their Response to Therapy

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Abstract

Objective To investigate the correlation of extraocular muscle and intraorbital fat involvement with diplopia and their responsiveness to intravenous glucocorticoid therapy in patients with thyroid-associated ophthalmopathy (TAO) using magnetic resonance imaging (MRI).

Methods Clinical records, laboratory indices, and imaging parameters were retrospectively collected from 195 patients with TAO (114 with diplopia and 81 without) and 30 contemporaneous patients with normal orbital MRI findings. Parameters, including extraocular muscle thickness, extraocular muscle volume, signal intensity ratio of the extraocular muscle (M-SIR, intraorbital fat volume (FV), SIR of intraorbital fat (F-SIR), and orbital volume (OV), were measured. Using univariate and multivariate logistic regression independent predictors of TAO-related diplopia and therapeutic efficacy were determined. The diagnostic performance of these indicators was assessed with receiver operating characteristic curves.

Results In total, 390 orbits (228 with diplopia, 162 without diplopia, and 60 normal controls) were analyzed. Most parameters were significantly higher in patients with TAO and diplopia compared with those without diplopia. However, stepwise multivariate logistic regression identified inferior rectus thickness, $M-SIR_{mean}$, FV/OV , and $F-SIR_{mean}$ as the independent risk factors with the highest diagnostic value for TAO-related diplopia. The combined index of these indicators showed superior diagnostic performance compared with individual parameters. Similarly, $M-SIR_{mean}$ and $F-SIR_{mean}$ were identified as independent determinants of therapeutic responsiveness for diplopia using stepwise multivariate logistic regression.

Conclusions TAO-related diplopia and its therapeutic outcomes are associated with extraocular muscle changes and intraorbital fat involvement. A comprehensive analysis of both structures can provide more objective evidence for clinical decision-making.

Introduction

Thyroid-associated ophthalmopathy (TAO), also known as Graves' ophthalmopathy, is an organ-specific autoimmune disorder and the most prevalent orbital disease in adults [1-3]. TAO presents with diverse clinical features, including eyelid retraction, proptosis, diplopia, and visual impairment [2,3]. Diplopia is the initial symptom in a subset of patients with TAO [4,5]. Studies have shown that patients with diplopia exhibit significantly poorer quality of life and greater levels of disability-related psychological distress than those without diplopia [5,6]. Current evidence indicates that diplopia primarily results from extraocular muscle involvement [7]. Therapeutic approaches include prism correction, pharmacotherapy, radiotherapy, and strabismus surgery; however, their efficacy remains inconsistent [8,9]. Objective, quantitative studies correlating extraocular muscle alterations with diplopia are limited. Clinically, we have observed associations between intraorbital fat changes and diplopia, as well as correlations between therapeutic response and changes in both extraocular muscles and intraorbital fat; however, these findings have not been comprehensively documented in the literature. Therefore, this study aimed to investigate the relationships among extraocular muscles, intraorbital fat, and diplopia in patients with TAO using quantitative

magnetic resonance imaging (MRI) metrics and to evaluate their correlation with glucocorticoid treatment efficacy. This approach could provide comprehensive imaging biomarkers for the clinical assessment of diplopia and support optimal treatment selection.

Methods

Study Population

This study complied with the principles of the Declaration of Helsinki. It was approved by the Institutional Review Board of the Eighth Affiliated Hospital of Southern Medical University with a waiver of informed consent, as it was a retrospective study (approval no. KYLS20220723).

This retrospective study enrolled patients diagnosed with TAO who underwent orbital MRI between August 2020 and February 2025 at the Eighth Affiliated Hospital of Southern Medical University. Individuals who concurrently underwent orbital MRI for other conditions and had normal results served as the control group.

Inclusion criteria for TAO patients were as follows: (1) diagnosis according to the Bartley criteria [10] and the 2022 Chinese Guidelines for TAO Diagnosis and Management [11]; (2) complete orbital MRI and clinical records; and (3) age ≥ 17 years. Patients were classified into diplopia and non-diplopia groups based on clinical symptoms. Those with TAO-related diplopia who completed intravenous glucocorticoid pulse therapy were further stratified into responder and non-responder groups. Responders were defined as having a ≥ 1 -grade improvement on the diplopia grading scale [12]. Diplopia was categorized into the following grades: Grade 0, no diplopia; Grade 1, transient diplopia; Grade 2, intermittent diplopia; Grade 3, persistent diplopia.

Inclusion criteria for controls were as follows: (1) no history of hyperthyroidism or other thyroid disorders, (2) complete orbital MRI and clinical documentation, (3) age ≥ 17 years.

Exclusion criteria for all participants included: (1) other ocular pathologies (e.g., retrobulbar masses), (2) other autoimmune diseases, (3) diabetic retinopathy, (4) hypertensive retinopathy, (5) history of orbital surgery (e.g., decompression), and (6) prior orbital radiotherapy.

From the initially screened 350 patients, 135 were excluded due to incomplete data, 13 for prior orbital surgery, and seven because of a history of radiotherapy. The final cohort included 195 patients (390 eyes): 114 (228 eyes) in the diplopia group, 81 (162 eyes) in the non-diplopia group, and 30 (60 eyes) in the control group. Of these, 34 patients with diplopia completed glucocorticoid therapy, comprising 11 responders (22 eyes) and 23 non-responders (46 eyes). Figure 1 presents a flow diagram of the participant selection process. Clinical parameters included age, sex, smoking history, thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), thyroglobulin (TG), thyrotropin receptor antibody (TRAb), thyroglobulin antibody (TGAAb), and thyroid peroxidase antibody (TPOAb).

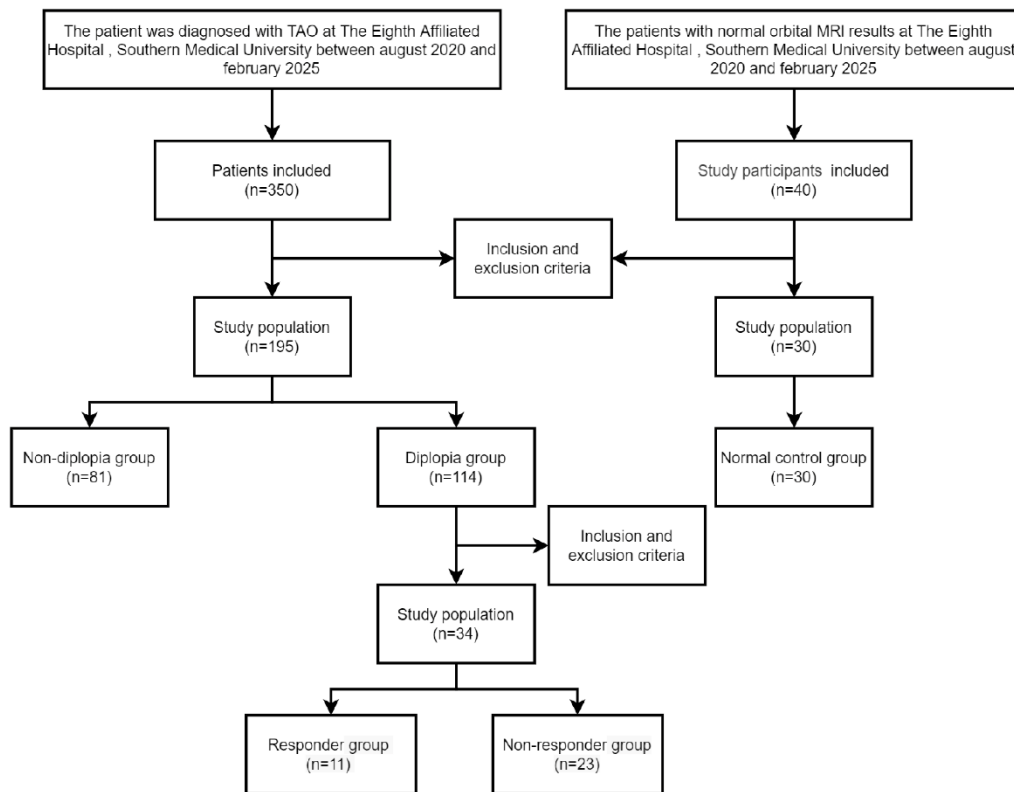


Fig.1 Flow diagram of study participant selection. TAO, thyroid-associated ophthalmopathy.

MRI Protocol

All examinations were performed on a 3.0-T MRI scanner (Siemens Skyra, Germany) using a 20-channel head coil, with coverage from the orbital apex to the optic chiasm. Coronal T2-weighted Dixon (T2WI-Dixon) and axial T1-weighted turbo spin-echo (T1WI-TSE) sequences were acquired.

T2WI-Dixon parameters were as follows

repetition time (TR) 4000 ms; echo time (TE) 91 ms; field of view (FOV) 150 × 150 mm²; matrix size 320 × 320; slice thickness 3 mm; interslice gap 0.6 mm; echo train length 21; parallel imaging factor (GRAPPA) 2; flip angle 150°; number of excitations (NEX) 2; bandwidth 381 Hz/pixel; scan time 3 min 32 s.

T1WI-TSE parameters were as follows

TR 756 ms; TE 7.1 ms; FOV 150 × 150 mm²; matrix size 256 × 256; slice thickness 3 mm; interslice gap 0.3 mm; echo train length 3; GRAPPA factor 2; flip angle 150°; NEX 3; bandwidth 305 Hz/pixel; scan time 1 min 36 s.

Image Analysis

1. Measurements of extraocular muscle thickness and signal intensity ratio (SIR)

Measurements were performed independently and randomly by two radiologists—one resident with 5 years of experience and one senior consultant with 20 years of experience—under single-masked conditions. On coronal in-phase T2WI-Dixon images,

the thicknesses of the superior rectus (SR), inferior rectus (IR), and medial rectus (MR) muscles were measured at their maximum thickness level (Figure. 2a). The lateral rectus (LR) thickness was measured at its maximal thickness on axial T1WI-TSE images (Figure. 2b). Mean, minimum, and maximum signal intensity (SI) values of all extraocular muscle bellies and intraorbital fat were obtained from coronal water-phase T2WI-Dixon images using a region-of-interest (ROI) analysis (Figure. 2c and 2d). Ipsilateral cerebral white matter (WM) SI was measured using the same coronal water-phase T2WI-Dixon images (Figure. 2e). The SIR was calculated as the ratio of extraocular muscle or intraorbital fat to ipsilateral WM[13]. The mean, minimum, and maximum SIR values from all four extraocular muscles were averaged and denoted as M-SIR_{mean}, M-SIR_{min}, and M-SIR_{max}, respectively. Using the same approach, corresponding intraorbital fat parameters were calculated and denoted as F-SIR_{mean}, F-SIR_{min}, and F-SIR_{max}. SIR values reflect the degree of inflammatory edema in extraocular muscles and intraorbital fat. WM SI was measured using a circular 10-mm diameter ROI placed at the section displaying the maximal WM volume[14] (Figure. 2e).

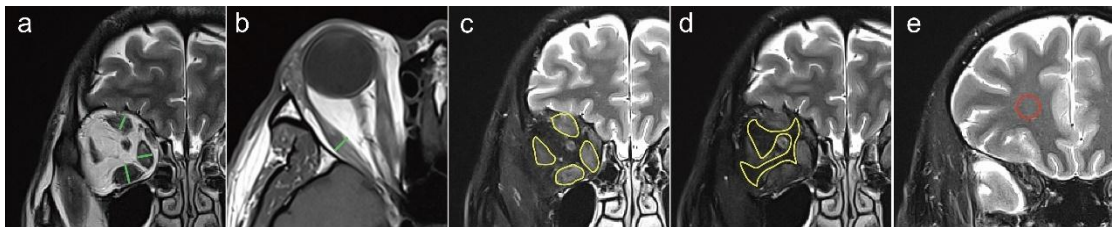


Figure.2 MRI-based quantification of extraocular muscle thickness, M-SIR, and F-SIR. A male TAO patient in his 40s with diplopia shows significant extraocular muscle hypertrophy on T2WI-Dixon sequences. **a** Coronal in-phase T2WI-Dixon image documenting thickness measurements of superior rectus (SR-T), inferior rectus (IR-T), and medial rectus (MR-T) at maximal cross-section (green lines). **b** Axial T1WI-TSE image documenting thickness measurements of lateral rectus (LR-T) at its maximal diameter (green line). **c**: Coronal water-phase T2WI-Dixon image for the measurement of SI of extraocular muscle bellies (yellow circles). **d**: Corresponding coronal water-phase T2WI-Dixon image showing intraorbital fat SI acquisition (yellow circles). **e**: Coronal water-phase T2WI-Dixon image for the measurement of SI of ipsilateral cerebral white matter (red circles). $SIR = SI_{(extraocular\ muscle\ or\ intraorbital\ fat)} / SI_{WM}$, SI, signal intensity.

2. Volumetric analysis of extraocular muscles, introbital fat, and orbits

DICOM-format MR images were imported into the ITK-SNAP software (version 4.0; <http://www.itknap.org>). A physician manually segmented the extraocular muscles, intraorbital fat, and orbital walls slice by slice along the tissue margins on MRI (Figures. 3a–c), generating the corresponding ROIs (Figures. 3d–f). Major blood vessels and lacrimal glands were systematically excluded during segmentation. A senior radiologist independently verified the results, and any discrepancies were resolved by consensus. The software automatically generated three-dimensional volumes of interest from the segmented structures (Figures. 3g–i). Volumetric data of the orbital tissues were automatically computed, and the extraocular muscle volume to orbital volume (EMV/OV) and fat volume to orbital volume (FV/OV) ratios were used to control for individual

differences.

$SIR = SI_{\text{(extraocular muscle or intraorbital fat)}} / SI_{WM}$

$M-SIR_{\text{mean}} = (SI_{SR\text{mean}}/SI_{WM} + SI_{IR\text{mean}}/SI_{WM} + SI_{MR\text{mean}}/SI_{WM} + SI_{LR\text{mean}}/SI_{WM}) / 4$ (The same approach was used for $M-SIR_{\text{min}}$ and $M-SIR_{\text{max}}$)

$F-SIR_{\text{mean}} = SI_{F\text{mean}}/SI_{WM}$ (the same approach was used for $F-SIR_{\text{min}}$ and $F-SIR_{\text{max}}$)

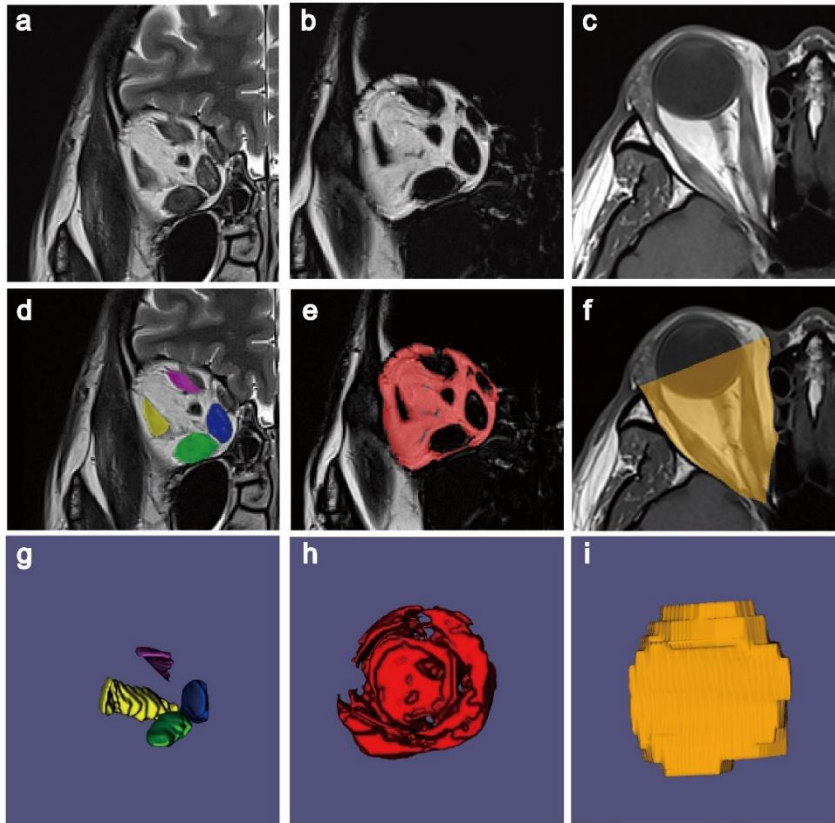


Figure.3 Segmentation of extraocular muscles, intraorbital fat, and orbital contours using ITK-SNAP. **a**, **b**: Coronal fat-phase T2WI-Dixon images. **c**: Axial T1WI-TSE image. **d**: Slice-by-slice manual delineation of extraocular muscles on coronal T2WI-Dixon: superior rectus (blue), inferior rectus (purple), medial rectus (pink), lateral rectus (green). **e**: Corresponding manual segmentation of intraorbital fat contours on coronal T2WI-Dixon. **f**: Axial T1WI-TSE image showing slice-wise delineation of orbital walls. **g**: 3D volume rendering of extraocular muscles VOI. **h**: 3D volume rendering of intraorbital fat VOI. **i**: 3D volume rendering of orbital VOI. VOI: volume of interest.

Statistical Analysis

Statistical analyses were performed using SPSS (version 27.0; IBM) and GraphPad Prism (version 9.5.0; GraphPad Software) for statistical computation and visualization. The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Normally distributed data were expressed as mean $\pm$ standard deviation, whereas non-normally distributed data are presented as medians with interquartile range (IQR; 25th–75th percentiles). Categorical variables are reported as frequencies or percentages.

Intergroup comparisons of normally distributed continuous variables were performed using one-way analysis of variance. Non-normally distributed data were analyzed using Mann-Whitney U tests (two groups) or Kruskal-Wallis H tests (≥ 3 groups), with Dunn's post-hoc test applied when appropriate. Categorical data were analyzed using the Chi-square (χ^2) or Fisher's exact tests. Univariate logistic regression was performed, followed by multivariate analysis, with diplopia status (presence or absence) and glucocorticoid treatment response (responder or non-responder) as binary outcome variables. Stepwise regression was used for variable selection in the multivariable models. Independent predictors were identified by computing odds ratios with 95% confidence intervals (CIs). Diagnostic performance was evaluated with receiver operating characteristic (ROC) curve analysis, and optimal cutoff values were determined using the method of maximizing Youden's index. Statistical significance was defined as two-tailed p-values < 0.05 .

Results

Demographic Characteristics

No significant differences in sex distribution or smoking history were observed among the diplopia, non-diplopia, and control groups ($p > 0.05$). However, age differed significantly among the groups ($p < 0.05$) (Table 1). Post hoc pairwise comparisons showed no significant age differences between the control group and either the diplopia or non-diplopia groups ($p > 0.05$). In contrast, patients in the diplopia group were significantly older than those in the non-diplopia group ($p < 0.05$) (Figure. 4). No significant differences in age, sex, or smoking history were observed between the responder and non-responder groups ($p > 0.05$) (Table 1).

Table 1 Comparison of demographic characteristics

Variables	Diplopia group (n=114)	Non-diplopia group (n=81)	Control group (n=30)	<i>p</i>	Responder group (n=11)	Non- responder group (n=23)	<i>p</i>
Age/years	49.00(40.25,56.75)	37.00(31.00,49.00)	45.00(30.50,59.75)	<0.001	47.36 $\pm$ 10.39	45.57 $\pm$ 14.27	0.712
sex/n(%)				0.065			0.477
Male	69(60.53)	37(45.68)	13(43.33)		7 (63.64)	11 (47.83)	
Female	45(39.47)	44(54.32)	17(56.67)		4 (36.36)	12 (52.17)	
Smoking history /n(%)				0.091			0.705
no	78(68.42)	66(81.48)	24(80.00)		8 (72.73)	14 (60.87)	
yes	36(31.58)	15(18.52)	6(20.00)		3 (27.27)	9 (39.13)	

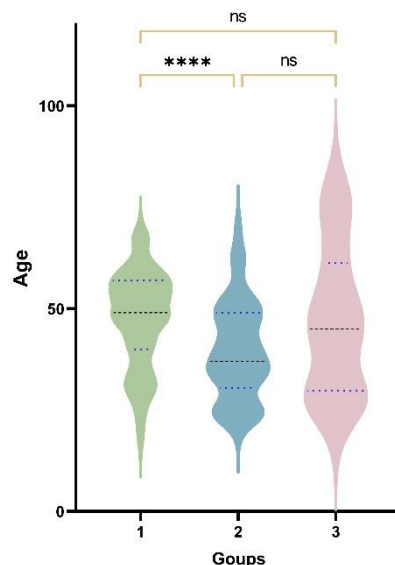


Figure.4 Violin plots for comparison of age among groups. Group 1, Diplopia group; Group 2, Non-diplopia group; Group 3, Control group

Thyroid Function and Antibody Profiles

No significant differences in TSH, FT3, FT4, TG, TRAb, TGAb, or TPOAb levels were observed between the diplopia and non-diplopia groups or between the responder and non-responder groups ($p > 0.05$). (Table 2). The control group exhibited normal thyroid function and was excluded from thyroid-related comparisons.

Table 2 Comparison of thyroid function and antibody profiles

Variables	Diplopia group (n=114)	Non-diplopia group (n=81)	p	Responder group (n=11)	Non-responder group (n=23)	p
TSH(mIU/L)	1.02 (0.01, 3.68)	0.77 (0.01, 3.02)	0.611	2.02 (0.20, 4.58)	1.10 (0.19, 2.75)	0.429
FT3(pmol/L)	5.34 (4.62, 6.27)	5.42 (4.88, 6.27)	0.490	4.94 (4.45, 6.63)	5.32 (4.70, 5.90)	0.568
FT4 (pmol/L)	11.43 (8.60, 14.28)	10.82 (9.07, 14.09)	0.913	7.83 (7.22, 16.80)	11.72 (8.57, 12.75)	0.632
TG (μg/L)	18.59 (1.23, 80.16)	26.45 (4.14, 128.97)	0.340	5.84 (1.48, 70.22)	26.63 (0.13, 94.00)	0.836
TRAb(IU/L)	5.22 (1.76, 15.85)	3.34 (1.23, 11.18)	0.089	5.96 (1.31, 10.58)	3.91 (2.20, 8.02)	0.663
TGAb (IU/mL)	0.40 (0.10, 18.73)	0.30 (0.10, 6.65)	0.312	3.40 (0.30, 54.35)	3.00 (0.38, 88.38)	0.767
TPOAb (IU/mL)	21.50 (1.10, 244.80)	10.80 (1.10, 115.90)	0.459	50.15 (7.55, 257.77)	11.60 (4.05, 57.52)	0.350

TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; TG, thyroglobulin; TRAb, thyrotropin receptor antibody; TGAb, thyroglobulin antibody;

TPOAb, thyroid peroxidase antibody

Imaging Characteristics

Significant differences in SR-T, IR-T, MR-T, LR-T, M-SIR_{mean}, M-SIR_{min}, M-SIR_{max}, EMV/OV, FV/OV, F-SIR_{mean}, F-SIR_{min}, and F-SIR_{max} were observed among the diplopia, non-diplopia, and control groups ($p < 0.001$) (Table 3). Significant differences were found between the diplopia and non-diplopia groups in IR-T, MR-T, M-SIR_{mean}, M-SIR_{min}, M-SIR_{max}, EMV/OV, FV/OV, F-SIR_{mean}, F-SIR_{min}, and F-SIR_{max} ($p < 0.05$). In contrast, SR-T and LR-T showed no significant differences ($p > 0.05$) (Figure. 5).

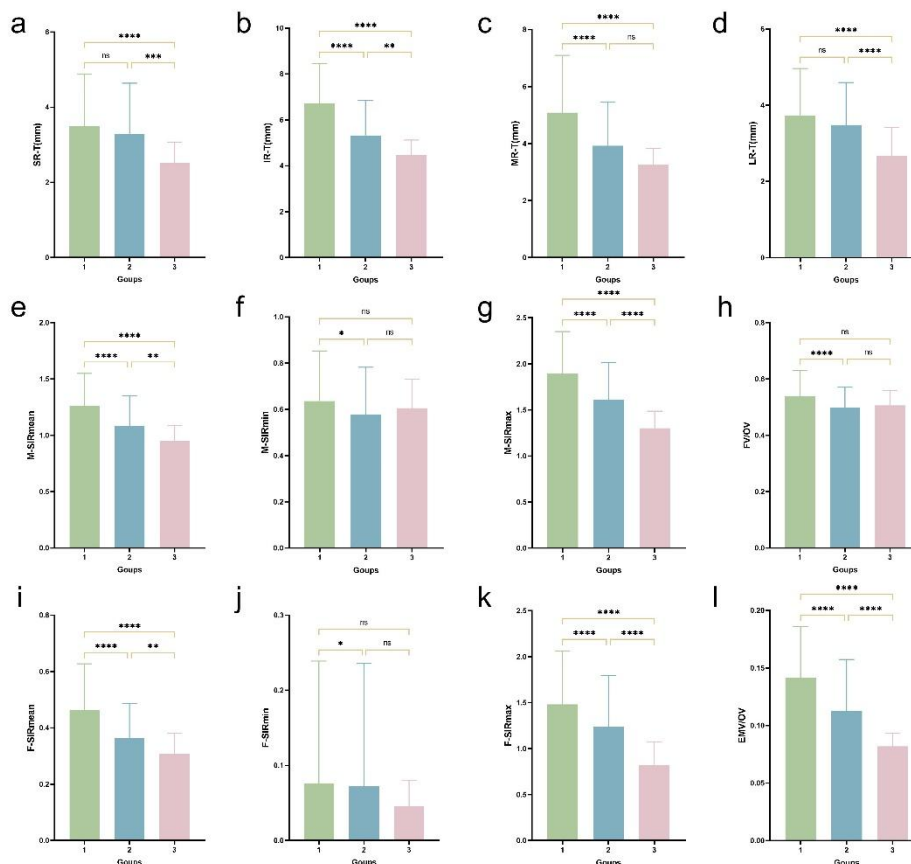
Significant differences in M-SIR_{mean}, M-SIR_{min}, M-SIR_{max}, F-SIR_{mean}, and F-SIR_{max} were observed between the responder and non-responder groups ($p < 0.05$). In contrast, SR-T, IR-T, MR-T, LR-T, FV/OV, EMV/OV, or F-SIR_{min} showed no significant differences ($p > 0.05$) (Table 3).

Table 3 Comparison of imaging characteristics

Variables	Diplopia group (n=228)	Non-diplopia group (n=162)	Control group (n=60)	p	Responder group (n=22)	Non-responder group (n=46)	p
SR-T(mm)	3.20 (2.40,4.30)	3.10 (2.30,3.90)	2.50 (2.18,2.90)	<.001	3.20 (2.12, 5.25)	3.10 (2.20, 4.10)	0.499
IR-T(mm)	6.90 (5.27,8.10)	4.95 (4.30,6.18)	4.35 (4.00,4.80)	<.001	7.60 (6.75, 8.78)	6.80 (5.23, 8.07)	0.082
MR-T(mm)	4.60 (3.50,6.30)	3.30 (2.90,4.40)	3.30 (2.90,3.60)	<.001	5.05 (4.08, 5.50)	4.00 (3.30, 5.90)	0.208
LR-T(mm)	3.50 (2.80,4.20)	3.30 (2.90,4.00)	2.55 (2.08,3.10)	<.001	3.50 (2.85, 3.88)	3.00 (2.52, 3.60)	0.064
M-SIR _{mean}	1.23 (1.04,1.45)	1.00 (0.90,1.23)	0.95 (0.89,1.03)	<.001	1.44 (1.34, 1.60)	1.20 (1.08, 1.36)	<.001
M-SIR _{min}	0.61(0.49,0.77)	0.56 (0.45,0.71)	0.60 (0.54,0.65)	0.039	0.84 (0.78, 0.99)	0.72 (0.62, 0.80)	<.001
M-SIR _{max}	1.88(1.56,2.20)	1.54 (1.30,1.81)	1.30 (1.20,1.40)	<.001	2.11 (1.80, 2.20)	1.71 (1.55, 2.00)	0.001
FV/OV	0.52 (0.47,0.59)	0.49 (0.46,0.54)	0.50 (0.47,0.53)	<.001	0.50 (0.46, 0.53)	0.47 (0.44, 0.51)	0.071
EMV/OV	0.13(0.11,0.17)	0.10 (0.08,0.12)	0.08 (0.07,0.09)	<.001	0.14 (0.12, 0.16)	0.13 (0.10, 0.16)	0.237
F-SIR _{mean}	0.45 (0.35,0.54)	0.35 (0.28,0.41)	0.31 (0.26,0.36)	<.001	0.46 (0.38, 0.51)	0.38 (0.31, 0.46)	0.006
F-SIR _{min}	0.05 (0.02,0.09)	0.03 (0.01,0.07)	0.03 (0.02,0.06)	0.020	0.03 (0.01, 0.05)	0.03 (0.01, 0.06)	0.607

F-SIR _{max}	1.39 (1.07,1.77)	1.11(0.85,1.57)	0.79 (0.62,0.95)	<.001	1.56 (1.32, 2.36)	1.28 (1.02, 1.57)	0.004
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226 SR-T (mm), Superior rectus thickness in millimeters; IR-T (mm), Inferior rectus thickness
 227 in millimeters; MR-T (mm), Medial rectus thickness in millimeters; LR-T (mm), Lateral
 228 rectus thickness in millimeters; M-SIR_{mean}, Mean signal intensity ratio of extraocular
 229 muscles to ipsilateral white matter; M-SIR_{min}, Minimum signal intensity ratio of extraocular
 230 muscles to ipsilateral white matter; M-SIR_{max}, Maximum signal intensity ratio of
 231 extraocular muscles to ipsilateral white matter; EMV/OV, Ratio of extraocular muscle
 232 volume to orbital volume; FV/OV, Ratio of intraorbital fat volume to orbital volume; F-
 233 SIR_{mean}, Mean signal intensity ratio of intraorbital fat to ipsilateral white matter; F-SIR_{min},
 234 Minimum signal intensity ratio of intraorbital fat to ipsilateral white matter; F-SIR_{max},
 235 Maximum signal intensity ratio of intraorbital fat to ipsilateral white matter



236
 237 **Figure.5** Differences in imaging characteristics among groups1-3. Group 1, Diplopia
 238 group; Group 2, Non-diplopia group; Group 3, Control group; SR-T (mm), Superior rectus
 239 thickness in millimeters; IR-T (mm), Inferior rectus thickness in millimeters; MR-T (mm),
 240 Medial rectus thickness in millimeters; LR-T (mm), Lateral rectus thickness in millimeters;
 241 M-SIR_{mean}, Mean signal intensity ratio of extraocular muscles to ipsilateral white matter;
 242 M-SIR_{min}, Minimum signal intensity ratio of extraocular muscles to ipsilateral white matter;
 243 M-SIR_{max}, Maximum signal intensity ratio of extraocular muscles to ipsilateral white
 244 matter; EMV/OV, Ratio of extraocular muscle volume to orbital volume; FV/OV, Ratio of
 245 intraorbital fat volume to orbital volume; F-SIR_{mean}, Mean signal intensity ratio of
 246 intraorbital fat to ipsilateral white matter; F-SIR_{min}, Minimum signal intensity ratio of

intraorbital fat to ipsilateral white matter; F-SIR_{max}, Maximum signal intensity ratio of intraorbital fat to ipsilateral white matter

Independent Predictors of Diplopia and Treatment Response

Variables showing significant differences between the diplopia and non-diplopia groups were entered into univariate logistic regression. Based on prior evidence linking TRAb levels to TAO activity and severity, TRAb was also included in the univariate analysis. Parameters with $p < 0.20$ were entered into the multivariable logistic regression using stepwise selection. IR-T, M-SIR_{mean}, FV/OV, and F-SIR_{mean} emerged as independent risk factors for diplopia (Table 4).

Variables that differed significantly between the responder and non-responder groups underwent univariate logistic regression. Parameters with $p < 0.05$ were entered into the multivariable logistic regression using stepwise selection. M-SIR_{mean} and F-SIR_{mean} were identified as independent predictors of therapeutic response (Table 4).

Table 4 Logistic regression analysis of diplopia and its therapeutic response

Variables	univariable logistic regression			multivariable logistic regression			univariable logistic regression			univariable logistic regression		
	OR(95%CI)	Z	P	OR(95%CI)	Z	P	OR(95%CI)	Z	P	OR(95%CI)	Z	P
Age(years)	1.06 (1.04 ~ 1.08)	6.09	<.001									
TRAb(IU/L)	1.01 (0.99 ~ 1.03)	1.37	0.171									
IR-T(mm)	1.68 (1.46 ~ 1.93)	7.23	<.001	1.45 (1.23 ~ 1.71)	4.42	<.001						
MR-T(mm)	1.47 (1.28 ~ 1.68)	5.60	<.001									
M-SIR _{mean}	1.27 (1.17 ~ 1.38)	5.66	<.001	1.12 (1.01 ~ 1.24)	2.02	0.043	1.53 (1.17 ~ 1.98)	3.16	0.002	1.39 (1.05 ~ 1.83)	2.33	0.020
M-SIR _{max}	1.14 (1.03 ~ 1.26)	2.63	0.009				1.70 (1.21 ~ 2.39)	3.05	0.002			
M-SIR _{min}	1.17 (1.11 ~ 1.23)	5.78	<.001				1.25 (1.06 ~ 1.49)	2.57	0.010			
FV/OV	1.80 (1.38 ~ 2.35)	4.33	<.001	2.54 (1.84 ~ 3.50)	5.65	<.001						
EMV/OV	5.07 (2.91 ~ 8.82)	5.74	<.001									
F-SIR _{mean}	1.70 (1.43 ~ 2.03)	5.89	<.001	1.46 (1.17 ~ 1.81)	3.42	<.001	2.01 (1.24 ~ 3.27)	2.82	0.005	1.68 (1.04 ~ 2.70)	2.14	0.033
F-SIR _{max}	1.08 (1.04 ~ 1.12)	3.97	<.001				1.14 (1.04 ~ 1.26)	2.75	0.006			
F-SIR _{min}	1.02 (0.90 ~ 1.15)	0.26	0.796									

OR, Odds ratio; CI, Confidence interval; TRAb(IU/L), Thyrotropin receptor antibody; IR-T (mm), Inferior rectus thickness in millimeters; MR-T (mm), Medial rectus thickness in millimeters; M-SIR_{mean}, Mean signal intensity ratio of extraocular muscles to ipsilateral white matter; M-SIR_{min}, Minimum signal intensity ratio of extraocular muscles to ipsilateral white matter; M-SIR_{max}, Maximum signal intensity ratio of extraocular muscles to ipsilateral white matter; EMV/OV, Ratio of extraocular muscle volume to orbital volume; FV/OV, Ratio of intraorbital fat volume to orbital volume; F-SIR_{mean}, Mean signal intensity ratio of intraorbital fat to ipsilateral white matter; F-SIR_{min}, Minimum signal intensity ratio of intraorbital fat to ipsilateral white matter; F-SIR_{max}, Maximum signal intensity ratio of intraorbital fat to ipsilateral white matter

Optimal Cutoff Values for Discriminating Diplopia and Its Therapeutic Response

The ROC analysis of IR-T, M-SIR_{mean}, FV/OV, and F-SIR_{mean} yielded AUCs of 0.732 (95% CI: 0.682–0.783), 0.688 (95% CI: 0.634–0.741), 0.626 (95% CI: 0.570–0.681), and 0.704 (95% CI: 0.652–0.755), respectively (all > 0.5, indicating diagnostic significance). The combined index of these predictors demonstrated a significantly superior discriminatory ability (AUC = 0.811; 95% CI: 0.769–0.854) compared to the individual parameters, with a sensitivity of 75.3%, specificity of 76.3%, and an optimal cutoff of 0.557 (determined by Youden's index). This combination achieved the highest diagnostic performance (Figure. 6, Table 5).

Similarly, the ROC analysis of M-SIR_{mean} and F-SIR_{mean} yielded AUCs of 0.784 (95% CI: 0.672–0.895) and 0.714 (95% CI: 0.585–0.844), respectively (both > 0.5, indicating diagnostic significance). The combined index demonstrated a higher AUC (0.888; 95% CI: 0.812–0.964) than the individual parameters, with a sensitivity of 76.0%, specificity of 94.4%, and an optimal cutoff of 0.219 (Youden's index). This index achieved the highest diagnostic performance (Figure. 6, Table 5).

Table 5 Diagnostic performance of individual and combined index for diplopia and its therapeutic response

Variables	AUC (95%CI)	Accuracy (95%CI)	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	Cut off
diplopia							
IR-T(mm)	0.732 (0.682-0.783)	0.677 (0.628-0.723)	0.796 (0.734 - 0.858)	0.592 (0.528 - 0.656)	0.581 (0.516 - 0.646)	0.804 (0.743 - 0.864)	6.45
M-SIR _{mean}	0.688 (0.634-0.741)	0.679 (0.631-0.726)	0.519 (0.442 - 0.595)	0.794 (0.741 - 0.846)	0.641 (0.559 - 0.723)	0.699 (0.643 - 0.755)	1.014
FV/OV	0.626 (0.570-0.681)	0.610 (0.560-0.659)	0.611 (0.536 - 0.686)	0.610 (0.546 - 0.673)	0.527 (0.455 - 0.598)	0.688 (0.624 - 0.752)	0.504
F-SIR _{mean}	0.704 (0.652-0.755)	0.677 (0.628-0.723)	0.747 (0.680 - 0.814)	0.627 (0.564 - 0.690)	0.587 (0.520 - 0.655)	0.777 (0.717 - 0.837)	0.41
combined index	0.811 (0.769-0.854)	0.759 (0.713-0.801)	0.753 (0.687 - 0.819)	0.763 (0.708 - 0.818)	0.693 (0.625 - 0.761)	0.813 (0.761 - 0.865)	0.557
Therapeutic Response							
M-SIR _{mean}	0.784 (0.672-0.895)	0.721 (0.599-0.823)	0.609 (0.468 - 0.750)	0.955 (0.868 - 1.000)	0.966 (0.899 - 1.000)	0.538 (0.382 - 0.695)	6.45
F-SIR _{max}	0.714 (0.585-0.844)	0.676 (0.552-0.785)	0.652 (0.515 - 0.790)	0.727 (0.541 - 0.913)	0.833 (0.712 - 0.955)	0.500 (0.327 - 0.673)	0.452
combined index	0.792 (0.686-0.897)	0.750 (0.630-0.847)	0.761 (0.638 - 0.884)	0.727 (0.541 - 0.913)	0.854 (0.745 - 0.962)	0.593 (0.407 - 0.778)	0.219

IR-T (mm), Inferior rectus thickness in millimeters; M-SIR_{mean}, Mean signal intensity ratio of extraocular muscles to ipsilateral white matter; FV/OV, Ratio of intraorbital fat volume to orbital volume; F-SIR_{mean}, Mean signal intensity ratio of intraorbital fat to ipsilateral white matter; AUC, Area under the ROC curve; CI, Confidence interval;

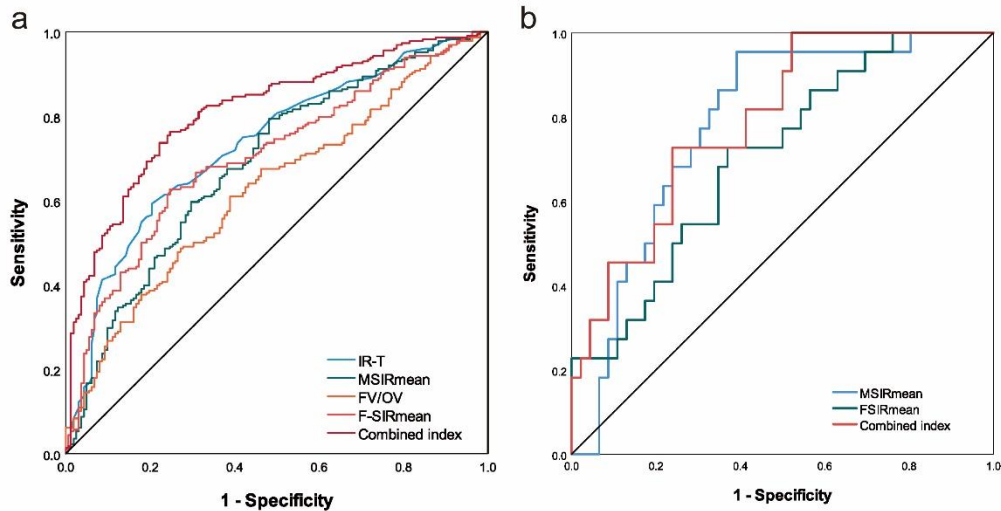


Figure.6 ROC Curves for Discriminating Diplopia and Its Therapeutic Response
a, ROC curves of individual and combined index (IR-T, M-SIR_{mean}, FV/OV, F-SIR_{mean}) for assessing Diplopia. **b**, ROC curves of individual and combined index (M-SIR_{mean}, F-SIR_{mean}) for assessing therapeutic response. IR-T (mm), Inferior rectus thickness in millimeters; M-SIR_{mean}, Mean signal intensity ratio of extraocular muscles to ipsilateral white matter; FV/OV, Ratio of intraorbital fat volume to orbital volume; F-SIR_{mean}, Mean signal intensity ratio of intraorbital fat to ipsilateral white matter; ROC, Receiver operating characteristic

Discussion

Diplopia substantially impairs quality of life in patients with TAO. However, clinical evidence regarding its risk factors and therapeutic outcomes remains limited. This study investigated objective risk factors for diplopia and independent predictors of glucocorticoid treatment efficacy through quantitative analysis of extraocular muscles, intraorbital fat, clinical parameters, and laboratory indices in patients with TAO. IR-T, M-SIR_{mean}, FV/OV, and F-SIR_{mean} were identified as independent risk factors for diplopia, whereas M-SIR_{mean} and F-SIR_{mean} predicted treatment response. This study provides evidence linking intraorbital fat changes to the development of diplopia and treatment efficacy, thereby offering novel therapeutic insights.

1 Advantages of the Dixon Technique in TAO Assessment

MRI provides superior soft tissue contrast and multiparametric imaging capabilities without ionizing radiation, making it a cornerstone for TAO assessment [15]. Compared to CT and ultrasound, MRI more clearly delineates inflammatory changes in the complex, small-volume orbital structures [16–18]. Unlike previous studies that utilized fat-suppressed (FS) or short tau inversion recovery sequences to eliminate orbital fat inflammation [19], we employed T2WI-Dixon sequences. This technique offers exceptional water-fat separation and is well established for quantitative tissue characterization[20]. T2WI-Dixon also provides low susceptibility artifacts, high sensitivity to inflammatory changes, and rapid acquisition—attributes ideal for orbital imaging [21,22]. Our previous study[23] confirmed that T2WI-Dixon water-phase images outperformed T2WI-SPAIR in image quality, enabling superior evaluation of retrobulbar inflammatory edema in TAO.

2 Association of Extraocular Muscle Parameters with Diplopia

Significant differences in rectus muscle thickness were observed among the control, non-diplopia, and diplopia groups, with particularly pronounced differences in IR-T and MR-T between the diplopia and non-diplopia groups. This aligns with established evidence that the IR and MR are the most frequently affected muscles in TAO [24–27]. Significant EMV/OV differences across the three groups further suggest that diplopia severity correlates with progressive extraocular muscle (EOM) enlargement. Autoimmune attacks trigger hyaluronan accumulation and cytokine overexpression, inducing lymphoplasmacytic infiltration within the endomysium, which exacerbates inflammation and volumetric expansion [28]. Consequently, inflammatory impairment of EOM function likely restricts ocular motility and causes diplopia. Furthermore, EOM enlargement reduces orbital compliance, further constraining ocular motility and promoting diplopia.

Significant intergroup differences in $M-SIR_{mean}$, $M-SIR_{min}$, and $M-SIR_{max}$ have also been documented, suggesting that SIR alterations correlate with diplopia development. Inflammation predominates during active TAO phases, whereas fibrosis and adipogenesis are characteristic of the inactive phase [29]. These pathophysiological changes alter tissue composition and directly influence SIR. Elevated $M-SIR_{mean}$, $M-SIR_{min}$, and $M-SIR_{max}$ in the diplopia group compared to the non-diplopia group likely reflect active-phase edema that disrupts EOM biomechanics, causing binocular misalignment and diplopia.

3 Association of Intraorbital Fat with Diplopia

In addition to extraocular muscle involvement, significant differences in FV/OV were observed between the diplopia and non-diplopia groups. Willem et al. [30] identified orbital fibroblasts as primary autoimmune targets of TAO. These mesenchymal stem cell-like progenitors exhibit multipotent differentiation capacity and differentiate into adipocytes under autoantibody or cytokine stimulation, driving intraorbital adipogenesis [31]. We propose that fat expansion reduces orbital compliance, mechanically restricts ocular motility, and causes diplopia. Previous studies have neglected fat–diplopia correlations; however, our findings help explain clinical observations of diplopia occurring without significant EOM enlargement.

Significant differences in $F-SIR_{mean}$, $F-SIR_{min}$, and $F-SIR_{max}$ were observed, with $F-SIR_{mean}$ emerging as an independent risk factor for diplopia. Meyer et al. [32] characterized TAO inflammation as OF-driven, noting aberrant expression of TG, TSH, and thyroid-related peptides. These molecules induce myofibroblast differentiation and promote extracellular matrix deposition and fibrotic remodeling. Elevated $F-SIR$ values in patients with diplopia likely reflect fat inflammation and fibrosis, which reduce tissue compliance and impair ocular biomechanics. These insights provide novel perspectives on diplopia pathogenesis and challenge current EOM-centric therapeutic paradigms.

4 Diagnostic Performance of Radiological Parameters for Diplopia

Nagy et al. [33] performed orbital MRI in 43 patients with TAO and diplopia and demonstrated that 95% exhibited EOM enlargement, confirming the association between EOM expansion and diplopia. However, intraorbital fat involvement was not investigated. We integrated IR-T, $M-SIR_{mean}$, FV/OV, and $F-SIR_{mean}$ into a combined index. ROC analysis demonstrated superior diagnostic performance for this index (AUC, 0.811), with a sensitivity of 75.3%, specificity of 76.3%, and a validated cutoff of 0.557. This model

provides an objective biomarker with a defined diagnostic threshold for clinical implementation.

5 Imaging Predictors of Treatment Response

No significant differences in demographics (age, sex, smoking history), thyroid indices (TSH, FT3, FT4, TG, TRAb, TGAAb, and TPOAb), or most imaging parameters (SR-T, IR-T, MR-T, LR-T, EMV/OV, FV/OV, and F-SIR_{min}) were observed between the responder and non-responder groups. Significantly higher M-SIR_{mean}, M-SIR_{min}, and M-SIR_{max} in responders ($p < 0.05$) suggest that glucocorticoid efficacy correlates with greater EOM edema severity.

Significant differences in F-SIR_{mean} and F-SIR_{max} were observed, with F-SIR_{mean} identified as an independent predictor of therapeutic response. Higher F-SIR_{mean} in responders than in non-responders likely indicates intensified intraorbital fat inflammation, with edema-mediated signal elevation. Glucocorticoids effectively suppress this inflammatory cascade, reducing fat edema and SIR values, which explains the enhanced treatment response in patients with elevated M-SIR_{mean} and F-SIR_{mean}. These biomarkers provide critical guidance for therapeutic stratification.

Current TAO management remains challenging, as first-line intravenous glucocorticoids show suboptimal diplopia improvement in some patients and carry safety concerns. Therefore, patients with low M-SIR_{mean} and F-SIR_{mean} should be directed to second-line therapies to avoid ineffective glucocorticoid exposure. Mechanistically, IGF-1R and TSHR co-regulate the differentiation of orbital fibroblasts into hyaluronan-secreting adipocytes, thereby driving TAO pathogenesis. Teprotumumab, an IGF-1R inhibitor, significantly reduces proptosis, clinical activity score (CAS), and diplopia, while improving quality of life in moderate-to-severe active TAO [34,35].

6 Study Innovations and Limitations

This study has several innovations. First, based on clinical questions, previous studies have shown that diplopia in TAO is associated with extraocular muscle enlargement, while intraorbital fat is an additional risk factor for diplopia. Second, objective quantitative imaging indicators were utilized, demonstrating good reproducibility. Third, F-SIR was calculated as the ratio of signal enhancement in intraorbital fat to that in the ipsilateral cerebral white matter, revealing that F-SIR_{mean} is an independent predictor of the effectiveness of steroid therapy for diplopia. Finally, 3D imaging was employed to evaluate both the extraocular muscles and orbital fat.

However, this study has some limitations. For example, as this was a retrospective study, the data may be subject to selection bias. Our team plans to conduct prospective, multicenter, large-sample studies in the future to further investigate the intrinsic relationship between diplopia in TAO and imaging parameters.

Conclusion

In summary, diplopia in TAO is associated not only with extraocular muscle enlargement and SIR values, as reported in previous studies, but it is also closely correlated with FV and F-SIR. The effectiveness of first-line therapy for TAO-related diplopia is significantly linked to both extraocular muscles and orbital fat. Therefore, a comprehensive analysis of extraocular muscles and orbital fat provides a more thorough and objective basis for clinical practice, facilitating the selection of optimal treatment

strategies.

Abbreviations

TAO	Thyroid-associated ophthalmopathy
TSH	Thyroid-stimulating hormone
FT3	Free triiodothyronine
FT4	Free thyroxine
TG	Thyroglobulin
TRAb	Thyrotropin receptor antibody
TGAb	Thyroglobulin antibody
TPOAb	Thyroid peroxidase antibody
SR-T	Superior rectus thickness
IR-T	Inferior rectus thickness
MR-T	Medial rectus thickness
LR-T	Lateral rectus thickness
SI	Signal intensity
SIR	Signal intensity ratio
M-SIR _{mean}	Mean SIR of extraocular muscles
M-SIR _{min}	Minimum SIR of extraocular muscles
M-SIR _{max}	Maximum SIR of extraocular muscles
OV	Orbital volume
EMV/OV	Ratio of extraocular muscle volume to OV
FV/OV	Ratio of intraorbital fat volume to OV
F-SIR _{mean}	Mean SIR intraorbital fat
F-SIR _{min}	Minimum SIR of intraorbital fat
F-SIR _{max}	Maximum SIR of intraorbital fat
AUC	Area under the curve
ROC	Receiver operating characteristic curve
CI	Confidence interval

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Author contributions

HXC and JS contributed to the conception and design of the study. GFS, and XW coordinated the study. GFS, XW, DL, and MXZ acquired the data. XLG, XFL, and XLB did the statistical analysis, interpreted the data and verified the underlying data. GFS and XW wrote the drafting of the manuscript. YBD and SFZ critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

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Data availability

For reasons of patient privacy, the data sets analyzed in the current study are not publicly available, but it can be obtained from the corresponding author (13825553451@139.com) under reasonable requirements.

Declarations

Ethics approval and consent to participate

This study complied with the principles of the Declaration of Helsinki. It was approved by the Institutional Review Board of the Eighth Affiliated Hospital of Southern Medical University with a waiver of informed consent, as it was a retrospective study (approval no. KYLS20220723).

Consent for publication

All researchers agree to publish

Competing interests

The authors declare no competing interests.

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