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Original Article

Correlation between intraorbital structural alterations and diplopia in thyroid-associated ophthalmopathy: an MRI-based study

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Abstract: Objective: To investigate the correlation between intraorbital tissue structures and diplopia in patients with thyroid-associated ophthalmopathy (TAO) using magnetic resonance imaging (MRI) technology. Methods: A retrospective analysis was conducted on 228 patients with TAO who were diagnosed and treated at the Affiliated Hospital of Yunnan University between March 2021 and June 2024. Patients were divided into a diplopia group (n=105) and a non-diplopia group (n=123) based on the presence or absence of diplopia. Results: Logistic regression analysis showed that a higher thyroid-stimulating hormone receptor antibody (TRAb) level was an independent protective factor against diplopia in TAO, whereas increased thickness of the inferior rectus (IR), medial rectus (MR), and lateral rectus (LR), as well as greater extraocular muscle volume (EMV), were independent risk factors (all $P<0.05$). The areas under the ROC curve (AUCs) for TRAb, IR, EMV, MR, and LR in predicting diplopia were 0.909, 0.863, 0.834, 0.732, and 0.637, respectively. The combined model achieved an AUC of 0.986, indicating excellent predictive performance. Moreover, the duration of diplopia was positively correlated with IR, MR, and LR thickness. Conclusion: MRI enables quantitative evaluation of intraorbital structural alterations in TAO patients. When integrated with clinical characteristics, it provides valuable guidance for the early identification and intervention of diplopia.

Keywords: Thyroid-related eye disease, intraorbital tissue, diplopia, magnetic resonance imaging, risk factors, correlation

Introduction

Thyroid-associated ophthalmopathy (TAO), also known as Graves eye disease, is a specific autoimmune disease characterized by inflammation of the thyroid, orbital, and periorbital tissues. It represents the most prevalent orbital disease in adults [1, 2]. TAO presents with diverse clinical manifestations and may involve multiple intraorbital structures, including the extraocular muscles, orbital fat, lacrimal glands, and optic nerves. Typical symptoms encompass eyelid retraction, exophthalmos, diplopia, and visual impairment [3]. Among these, diplopia, which may appear as an initial symptom in some patients, primarily results from extraocular muscle involvement. It manifests as double or blurred vision, significantly compromising visual function. Furthermore, it frequently contributes to psychological distress, such as anxiety and depression, markedly diminishing patients' quality of life [4, 5].

Current clinical assessment of diplopia in TAO primarily relies on tools such as the Hertel exophthalmometer, ocular motility evaluation, and patient-reported symptoms. Although useful to some extent, these methods are inherently subjective, heavily dependent on examiner's experience, and lack the ability to quantitatively capture subtle pathological changes in extraocular muscles or their spatial relationships with adjacent tissues. These limitations can lead to delayed or suboptimal clinical deci-

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sion-making regarding disease severity, treatment selection, and prognosis.

In contrast, magnetic resonance imaging (MRI) provides superior soft-tissue contrast, multiplanar reconstruction, and functional imaging capabilities. It excels at delineating morphological alterations, structural anomalies, and signal intensity changes within the orbital contents of TAO patients. Consequently, MRI has become an indispensable tool for the diagnosis, evaluation of disease activity, and monitoring of therapeutic responses in TAO [6]. Given the constraints of conventional methods and the diagnostic potential of MRI, this study aims to systematically investigate the correlation between quantitative MRI parameters of orbital tissues and the presence of diplopia in TAO. The findings are expected to provide a more objective basis for early identification, risk stratification, and clinical management of diplopia in affected individuals.

Objects and methods

Study population

A retrospective analysis was conducted on 228 patients with TAO who were diagnosed and treated at the Affiliated Hospital of Yunnan University from March 2021 to June 2024. Inclusion criteria: (1) Diagnosis consistent with Bartley's criteria [7]; (2) Age ≥18 years; (3) Complete clinical and imaging data available. Exclusion criteria: (1) Presence of other ocular diseases; (2) Coexisting disorders that may cause diplopia and extraocular muscle thickening; (3) History of ocular surgery or radiotherapy; (4) Severe hepatic, renal, or cardiac dysfunction, or malignancy; (5) Coexisting autoimmune diseases; (6) Poor MRI image quality. This study was approved by the Ethics Committee of The Affiliated Hospital of Yunnan University.

Sample size estimation

Sample size was calculated using the events per variable (EPV) principle. Based on a preliminary analysis, 12 predictor variables were planned for multivariate Logistic regression analysis. With an EPV of 5-10 and an expected lesion incidence of 35%, the required sample size was estimated to range from 172 to 343 cases, meaning that at least 172 patients should be included.

Diagnostic criteria for diplopia

Patients presented with persistent or intermittent binocular diplopia. The direction of image displacement and the range of extraocular muscle involvement were determined using the red glass test. The deviation angle in nine gaze directions was quantitatively measured through a synoptophore examination to further evaluate the extent of visual function impairment.

Data collection

Clinical data were collected from the hospital's electronic information system, including age, sex, body mass index (BMI), disease duration, history of hypertension, diabetes, smoking, or corticosteroid pulse therapy, clinical activity score (CAS) [8], duration of diplopia, C-reactive protein (CRP), total cholesterol (TC), triglycerides (TG), glycated hemoglobin (HbA1c), free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), thyroid-stimulating hormone receptor antibody (TRAb), anti-thyroid peroxidase (anti-TPO), and MRI parameters.

MRI examination and image analysis

MRI was performed using a 1.5T MR scanner (GE in the United States). During image acquisition, patients were positioned supine with eyes closed naturally, the head centered, and the body kept as symmetrical as possible. The scanning protocol included axial T1WI and axial, coronal, and sagittal T2WI with fat suppression (FS).

Axis T1WI and T2WI-FS: Acquisition matrix 320×320, field of view (FOV) 20 cm, 20 slices, slice thickness 2.5 mm. Coronal T2WI-FS: acquisition matrix 224×320, FOV 18 cm, 18 slices, slice thickness 2.5 mm. Sagittal T2WI-FS: acquisition matrix 346×384, FOV 18 cm, 17 slices, slice thickness 2.5 m. Each scan was performed twice for consistency.

MRI images were independently analyzed by two experienced radiologists, and the final values were derived from the mean of their measurements. On coronal and axial T2WI-FS images, the thickest portions of the superior rectus (SR), inferior rectus (IR), medial rectus (MR), and lateral rectus (LR) muscles were identified, and the cross-sectional thickness was mea-

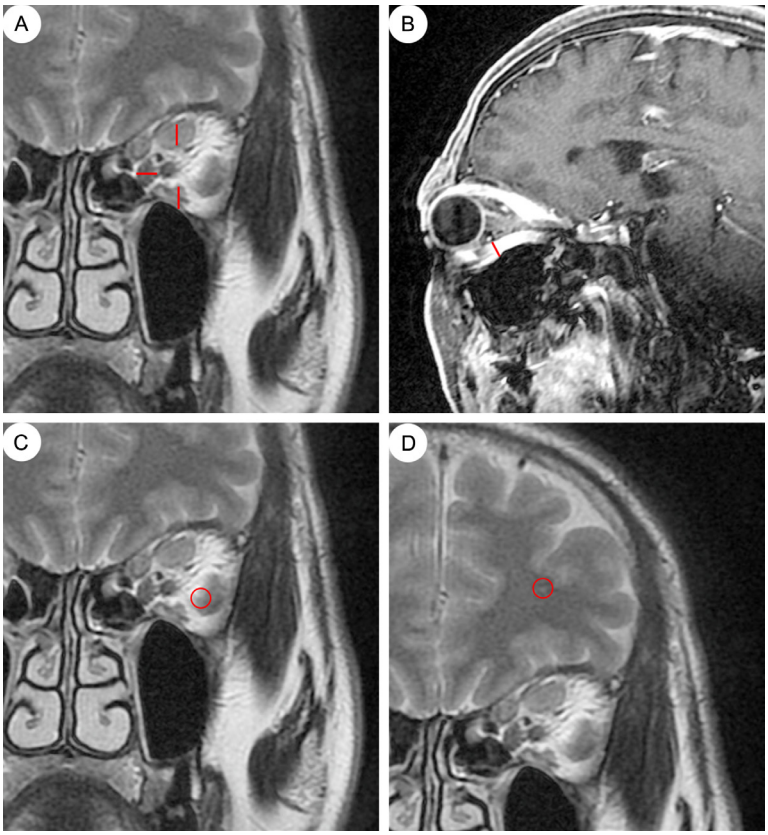

Figure 1. MRI imaging findings in a 52-year-old female patient with thyroid-associated ophthalmopathy (TAO) and diplopia. A: Measurement of the maximal thickness of the superior rectus, inferior rectus, and medial rectus muscles (red line segment) on coronal T2WI-FS sequence; B: Measurement of the maximal thickness of lateral rectus muscle (red line segment) on axial T2WI-FS sequence; C: Measurement of region of interest (ROI) at the area of highest signal intensity within the extraocular muscle belly (red circle) on coronal T2WI-FS sequence; D: Placement of the ROI at the area of strongest signal intensity within the ipsilateral cerebral white matter (red circle) on the coronal T2WI-FS sequence.

sured perpendicular to the muscle fiber axis (**Figure 1A**, **1B**). For signal intensity evaluation, a circular region of interest (ROI) of approximately 10 mm^2 was placed at the anterior central region of each extraocular muscle and the ipsilateral temporal white matter. The mean signal intensity ratio (SIR) of each muscle to white matter was calculated, and the maximum SIR value for each muscle was defined as SIRmax (**Figure 1C**, **1D**).

All MRI datasets were imported into ITK-SNAP 4.0 software. The boundaries of extraocular muscles, intraorbital fat, and bony orbit were manually delineated layer by layer by the same physician. The software automatically generated three-dimensional reconstructs and calculated the corresponding volumes of the extraocular muscles (EMV), intraorbital fat (IFV), and entire orbit (OV).

Statistical methods

All statistical analyses were performed using SPSS 26.0. Normally distributed quantitative data were described as mean ± standard deviation ($\bar{x} \pm sd$), and independent sample t-test was used for comparison between groups. Quantitative data not conforming to a normal distribution were expressed as median and interquartile range [M (P_{25}-P_{75})], and Wilcoxon rank-sum test was used for comparison between the groups. Categorical data were expressed as counts and percentages [n (%)], and the chi-square test was used to compare the differences between the groups. Logistic regression was used to identify independent factors associated with diplopia in TAO patients. The receiver operating characteristic (ROC) curve was used to evaluate the predictive value of these factors for diplopia. In addition, the Pearson correlation coefficient was used to assess the relationship between clinical parameters and the duration of diplopia. A two-tailed *P* value <0.05 was considered statistically significant.

Results

Comparison of general data

Among the 228 patients with TAO, 105 patients presented with diplopia and were included in the diplopia group, while 123 patients without diplopia were included in the non-diplopia group. There were no significant differences in sex, BMI, disease course, history of hypertension, diabetes, smoking, or corticosteroid pulse therapy between the two groups (P>0.05).

Table 1. Comparison of baseline information between the two groups

	Diplopia group (n=105)	Non-diplopia group (n=123)	t/χ^2	P
Age (years, $\bar{x}$ ± sd)	48.39±9.81	45.03±7.66	2.846	0.005
Sex [n (%)]			1.124	0.289
Male	67 (63.81)	70 (56.91)		
Female	38 (36.19)	53 (43.09)		
BMI (kg/m^2, $\bar{x}$ ± sd)	23.68±2.49	23.26±2.65	1.201	0.231
Disease course (months, $\bar{x}$ ± sd)	11.62±4.91	10.59±3.23	1.830	0.069
Hypertension [n (%)]			0.629	0.428
No	84 (80.00)	93 (75.61)		
Yes	21 (20.00)	30 (24.39)		
Diabetes [n (%)]			0.079	0.779
No	90 (85.71)	107 (86.99)		
Yes	15 (14.29)	16 (13.01)		
Smoking history [n (%)]			3.682	0.055
No	72 (68.57)	98 (79.67)		
Yes	33 (31.43)	25 (20.33)		
Corticosteroid pulse history [n (%)]			1.128	0.288
No	88 (83.81)	107 (86.99)		
Yes	19 (18.09)	16 (13.01)		
CAS (scores, $\bar{x}$ ± sd)	4.11±1.56	3.69±1.03	2.378	0.018

BMI: body mass index; CAS: clinical activity score.

Table 2. Comparison of laboratory data between the two groups

	Diplopia group (n=105)	Non-diplopia group (n=123)	t/Z	P
CRP (mg/L, $\bar{x}$ ± sd)	5.40±2.16	4.81±1.53	2.331	0.027
TC (mmol/L, $\bar{x}$ ± sd)	4.98±0.61	4.78±0.99	1.906	0.058
TG (mmol/L, $\bar{x}$ ± sd)	2.02±0.61	1.96±0.42	0.848	0.398
HbA1c (%, $\bar{x}$ ± sd)	6.17±0.81	6.00±0.65	1.701	0.091
FT3 (pmol/L, $\bar{x}$ ± sd)	4.64±1.31	4.46±0.91	1.187	0.237
FT4 (pmol/L, $\bar{x}$ ± sd)	15.10±3.80	14.59±2.91	1.131	0.259
TSH [mIU/L, M (P_{25}-P_{75})]	1.21 (0.31-2.29)	0.08 (0.03-1.42)	5.712	<0.001
TRAb (IU/L, $\bar{x}$ ± sd)	7.26±1.68	13.40±4.11	15.150	<0.001
anti-TPO [IU/mL, M (P_{25}-P_{75})]	46.00 (13.40-98.55)	31.00 (8.40-71.80)	2.996	0.003

CRP: C-reactive protein; TC: total cholesterol; TG: triglycerides; HbA1c: glycated hemoglobin; FT3: free triiodothyronine; FT4: free thyroxine; TSH: thyroid-stimulating hormone; TRAb: thyroid-stimulating hormone receptor antibody; anti-TPO: anti-thyroid peroxidase.

However, patients in the diplopia group were significantly older and had higher CAS compared with those in the non-diplopia group (P<0.05) (**Table 1**).

Comparison of laboratory data

No significant differences were observed between the two groups in TC, TG, HbA1c, FT3 and FT4 (P>0.05). In contrast, levels of CRP, TSH, TRAb, and anti-TPO were significantly higher in the diplopia group, whereas TSH levels were significantly lower, compared with the non-diplopia group (P<0.05) (**Table 2**).

Comparison of imaging data

There were no significant differences in OV or IFV/OV ratio between the two groups (*P*>0.05). However, the extraocular muscle thickness, SIR, SIRmax, EMV, and IFV in the diplopia group were significantly higher than those in the non-diplopia group (P<0.05) (**Table 3**).

Table 3. Comparison of MRI parameters between the two groups

	Diplopia group (n=105)	Non-diplopia group (n=123)	t	P
Extraocular muscle thickness (mm, $\bar{x}$ ± sd)				
SR	6.62±1.31	5.11±0.89	9.982	<0.001
IR	6.94±1.55	5.03±0.92	11.053	<0.001
MR	5.84±1.09	5.00±0.77	6.664	<0.001
LR	4.38±1.00	3.95±0.76	3.660	<0.001
SIR ($\bar{x}$ ± sd)	2.87±0.58	2.26±0.45	8.690	<0.001
SIRmax ($\bar{x}$ ± sd)	3.44±0.70	2.69±0.49	9.153	<0.001
EMV (mm^3, $\bar{x}$ ± sd)	13104.20±2475.67	10012.80±1962.77	10.322	<0.001
IFV (mm^3, $\bar{x}$ ± sd)	27171.83±4796.75	25863.10±4912.33	2.027	0.044
OV (mm^3, $\bar{x}$ ± sd)	41106.02±5964.10	40578.29±6074.03	0.659	0.510
IFV/OV ($\bar{x}$ ± sd)	0.67±0.14	0.65±0.16	1.034	0.302

SR: superior rectus; IR: inferior rectus; MR: medial rectus; LR: lateral rectus; SIR: signal intensity ratio; SIRmax: maximum signal intensity ratio; EMV: extraocular muscle volume; IFV: intraorbital fat volume; OV: orbital volume.

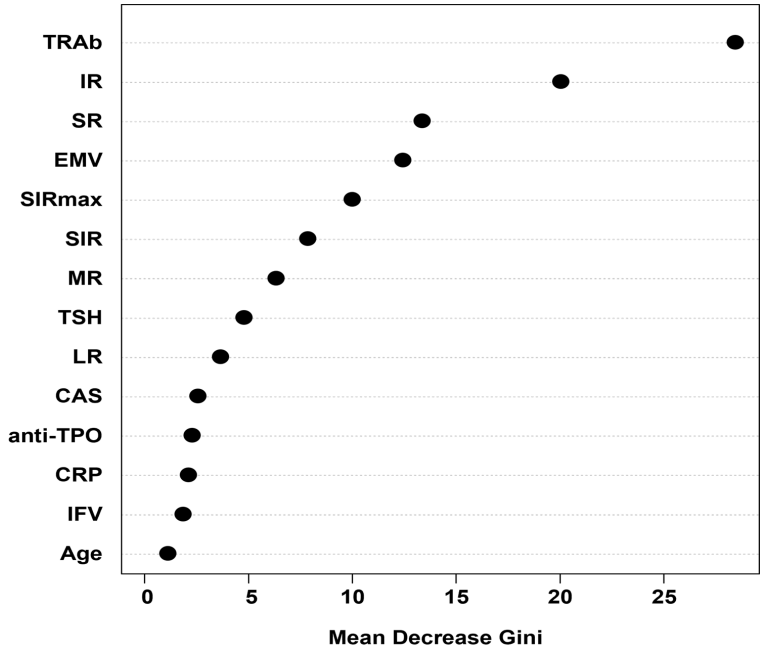

Figure 2. Screening of independent variables using random forest algorithm. TRAb: thyroid-stimulating hormone receptor antibody; IR: inferior rectus; SR: superior rectus; EMV: extraocular muscle volume; SIRmax: maximum signal intensity ratio; SIR: signal intensity ratio; MR: medial rectus; TSH: thyroid-stimulating hormone; LR: lateral rectus; CAS: clinical activity score; anti-TPO: anti-thyroid peroxidase; CRP: C-reactive protein; IFV: intraorbital fat volume.

Analysis of factors associated with diplopia in TAO

The presence of diplopia was taken as the dependent variable. Variables with statistical significance in the univariate analysis were screened using a random forest algorithm, and the top 10 predictors ranked by the Gini index were entered into a multivariate logistic regression model as independent variables (**Figure 2**). Considering its clinical relevance, age was also included as a covariate. Variable assignments for the regression analysis are shown in **Table 4**. Logistic regression analysis showed that higher TRAb level was an independent protective factor against diplopia in TAO ($P<0.05$), whereas increased thickness of the IR, MR, LR muscles, and greater EMV, were identified as independent risk factors (**Table 5**).

ROC curve analysis for predicting diplopia in TAO

ROC curve analyses were performed to evaluate the predictive value of TRAb, IR, EMV, MR, and LR, revealing the areas under the curve (AUCs) of 0.909, 0.863, 0.834, 0.732, and 0.637, respectively. The combined model incorporating TRAb, IR, EMV, MR, and LR reached an AUC of 0.956, indicating excellent predictive performance (**Figure 3** and **Table 6**).

Table 4. Assignment table

	Assignment
Whether double vision occurs	0= no, 1= yes
TRAb	Original value input
IR	Original value input
SR	Original value input
EMV	Original value input
SIRmax	Original value input
MR	Original value input
TSH	Original value input
LR	Original value input
CAS	Original value input
anti-TPO	Original value input
Age	Original value input

TRAb: thyroid-stimulating hormone receptor antibody; IR: inferior rectus; SR: superior rectus; EMV: extraocular muscle volume; SIRmax: maximum signal intensity ratio; MR: medial rectus; TSH: thyroid-stimulating hormone; LR: lateral rectus; CAS: clinical activity score; anti-TPO: anti-thyroid peroxidase.

Correlation analysis between independent factors with diplopia duration

The median duration of diplopia was 5.20 months, with an average of 4.89±1.72 months. Correlation analysis using the above risk factors as variables revealed that the duration of diplopia was positively correlated with the thickness of IR, MR, and LR muscles ($P<0.05$) (**Table 7**).

Discussion

In TAO, more than 90% of patients exhibit extraocular muscle involvement [9]. Diplopia in TAO is usually caused by abnormal tissue adhesion or traction following inflammatory involvement of the extraocular muscles, which restricts muscle contraction and relaxation functions and subsequently causes ocular motility disorders. These are mainly manifested as limitation of eye movement in the direction opposite to the affected muscle's primary action. In the early stage of TAO, peribulbar tissues are infiltrated by a large number of lymphocytes, and a variety of cytokines are produced to stimulate orbital fibroblast proliferation and glycosaminoglycan (GAG) synthesis. GAGs are highly hydrophilic and promote the infiltration of inflammatory cells such as neutrophils, lymphocytes, and macrophages, resulting in orbital connective tissue and extraocular muscle edema, elevated intraorbital pressure, and impaired muscle mobility. As the disease progresses to the chronic or fibrotic stage, the initial edema and lymphocyte infiltration are gradually replaced by fibroblast proliferation and collagen deposition, resulting in fibrotic adhesions within the extraocular muscles, and in severe cases, it may extend to involve the optic nerve, potentially causing compressive optic neuropathy [10-14]. In this study, 46.05% of patients developed diplopia. In contrast, Laurberg et al. [15] reported that among 216 patients with moderate-to-severe active TAO, the prevalence of diplopia was as high as 75.2%.

In the early evaluation of TAO, imaging techniques such as B-type ultrasound and CT were primarily used. These modalities provide two-dimensional images and can accurately depict morphological changes in the extraocular muscles; however, their ability to display posterior orbital fat and deep orbital structure is limited. CT examination diagnoses TAO mainly by identifying morphological changes in extraocular muscles and orbital adipose tissue, and is particularly effective in detecting bony changes or calcification. Nevertheless, CT offers limited information regarding disease staging and exposes patients to ionizing radiation [16-18]. In contrast, MRI possesses the advantages of multi-sequence, multi-planar imaging, and superior soft-tissue contrast resolution, enabling more precise delineation of intraorbital soft tissues compared with CT. MRI can clearly visualize subtle structural alterations and pathological lesions within the orbital contents of patients with TAO [19]. Owing to these technical advantages, MRI provides a more comprehensive and quantitative assessment of intraorbital tissues and delivers richer diagnostic information for analyzing the correlation between orbital structural changes and the occurrence of diplopia in TAO.

In this study, patients in the diplopia group showed marked MRI abnormalities, manifested as significant thickening of multiple extraocular muscles, increased signal intensity, and enlargement of both EMV and IFV, indicating a strong association between these imaging findings and the occurrence of diplopia. Importantly, the duration of diplopia was positively correlated with the thickness of the IR,

Table 5. Logistic regression analysis results

	β	SE	Wald χ^2	P	OR	95% CI
TRAb	-0.931	0.313	8.840	0.003	0.394	0.213-0.728
IR	2.158	0.696	9.612	0.002	8.656	2.212-33.872
SR	0.819	0.500	2.686	0.101	2.269	0.852-6.046
EMV	0.001	<0.001	8.099	0.004	1.001	1.000-1.002
SIRmax	1.461	0.860	2.890	0.089	4.312	0.800-23.253
MR	1.328	0.607	4.794	0.029	3.774	1.149-12.253
TSH	0.215	0.491	0.192	0.662	1.240	0.474-3.243
LR	1.884	0.701	7.215	0.007	6.581	1.664-26.023
CAS	-0.464	0.552	0.709	0.400	0.629	0.213-1.853
anti-TPO	0.001	0.013	0.009	0.925	1.001	0.976-1.027
Age	0.073	0.083	0.776	0.378	1.076	0.914-1.266

TRAb: thyroid-stimulating hormone receptor antibody; IR: inferior rectus; SR: superior rectus; EMV: extraocular muscle volume; SIRmax: maximum signal intensity ratio; MR: medial rectus; TSH: thyroid-stimulating hormone; LR: lateral rectus; CAS: clinical activity score; anti-TPO: anti-thyroid peroxidase.

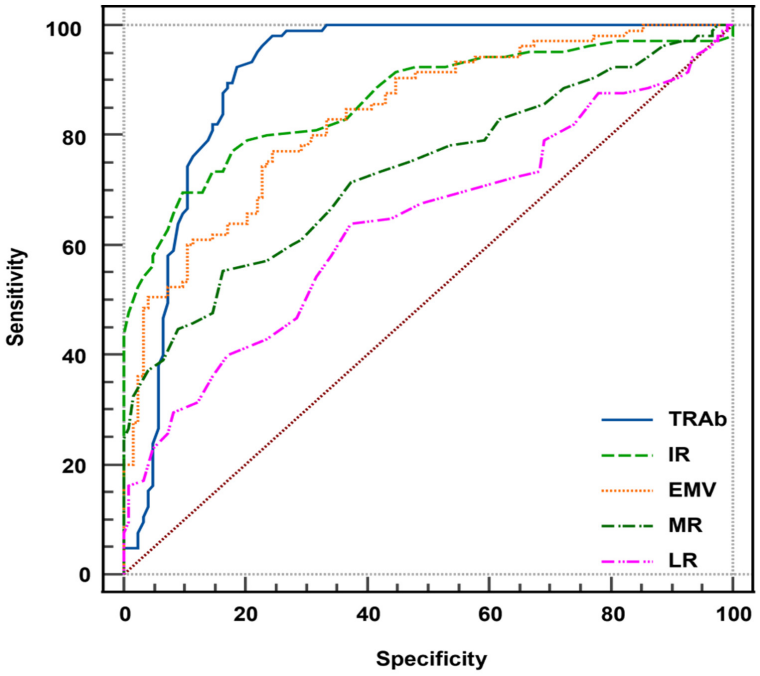

Figure 3. ROC curve analysis for TRAb, IR, EMV, MR, and LR in predicting diplopia occurrence in TAO. TRAb: thyroid-stimulating hormone receptor antibody; IR: inferior rectus; SR: superior rectus; EMV: extraocular muscle volume; MR: medial rectus; LR: lateral rectus; TAO: thyroid-associated ophthalmopathy.

MR and LR muscles. This observation has clear clinical implications, suggesting that the extraocular muscle thickening is not merely a static anatomical change but a dynamic marker reflecting the chronicity of functional impairment. The signal intensity on the T2WI image is directly proportional to the tissue water content. The fundamental pathological features of TAO include local tissue deterioration, exudation, and fibroblast proliferation, which can lead to increased interstitial water content, resulting in hyperintense extraocular muscles on T2WI during the active phase [20]. The observed muscle thickening and volume expansion mainly stem from inflammatory infiltration and GAG deposition, which collectively reduce muscle elasticity, increase rigidity, and enhance the local mass effect. Within the confined bony orbit, asymmetric enlargement of multiple extraocular muscles and the consequent rise in EMV significantly increase intraorbital pressure, limit normal muscle contraction and relaxation, disrupt binocular coordination through imbalance in muscle strength, motion amplitude, and synchrony [21, 22]. The positive correlation between diplopia duration and extraocular muscle thickness further suggests that prolonged structural remodeling contributes to progressive and irreversible mechanical restriction of ocular motility. Such restrictions prevent proper alignment of the visual axes and impair fusional capacity,

Table 6. Predictive value of independent factors for diplopia in TAO

	AUC	95% CI	Cut-off value	Youden Index	P	Sensitivity (%)	Specificity (%)
TRAb	0.909	0.864-0.943	10.2	0.737	<0.001	98.10	75.60
IR	0.863	0.811-0.905	6.2	0.598	<0.001	69.50	90.20
EMV	0.834	0.779-0.880	11261.1	0.528	<0.001	77.10	75.60
MR	0.732	0.670-0.789	5.7	0.390	<0.001	55.20	83.70
LR	0.637	0.571-0.699	4.1	0.264	<0.001	63.80	62.60
Combined diagnosis	0.986	0.921-0.999	-	0.791	<0.001	84.80	94.3

TRAb: thyroid-stimulating hormone receptor antibody; IR: inferior rectus; SR: superior rectus; EMV: extraocular muscle volume; MR: medial rectus; LR: lateral rectus; Combined diagnosis: TRAb+IR+EMV+MR+LR; TAO: thyroid-associated ophthalmopathy.

Table 7. Correlation analysis between duration of diplopia and various independent factors

	Duration of diplopia	
	r	P
TRAb	0.023	0.819
IR	0.497	<0.001
EMV	-0.073	0.462
MR	0.291	0.003
LR	0.197	0.044

TRAb: thyroid-stimulating hormone receptor antibody; IR: inferior rectus; SR: superior rectus; EMV: extraocular muscle volume; MR: medial rectus; LR: lateral rectus.

significantly increasing the likelihood of diplopia. Additionally, substantial muscle hypertrophy reduces the effective orbital space, further impeding normal globe movement [23]. TAO is driven by orbital fibroblast activation mediated by TSHR signaling. Elevated titers of TRAb activate TSHR-expressing orbital fibroblasts, promoting their proliferation and differentiation into mature adipocytes. This process increases retrobulbar soft tissue volume, exerts a forward mechanical force on the globe, and exacerbates ocular motility restriction, ultimately precipitating diplopia [24, 25]. Further analysis showed that the increased IR, MR, and LR thickness and higher EMV were independent risk factors for diplopia in TAO. These findings suggest that IR, MR, and LR are the most susceptible extraocular muscles to TAO-related involvement [21, 26, 27]. Moreover, EMV serves as a global indicator of intraorbital involvement: while thickening of an isolated muscle may not necessarily lead to diplopia, the overall increase in total muscle volume reflects compounded restriction within the confined orbital cavity, thereby significantly heightening the risk of ocular dyskinesia and diplopia [28].

In addition, higher TRAb levels were found to be an independent protective factor against diplopia in TAO patients. According to the common antigen theory of TAO, both the thyroid and postorbital soft tissues express TSHR, which can be activated by high titers of circulating TRAb, thereby initiating an autoimmune response. During this process, retroorbital fibroblasts, as core targets and effector cells, exhibit significant functional heterogeneity [29]. Based on the expression of the surface marker Thy-1 (CD90), orbital fibroblasts can be divided into two functionally distinct subgroups: Thy-1$^+$ fibroblasts, which are overexpressed in the orbit, can produce prostaglandin E2, IL-8, and large amounts of hyaluronic acid (HA) upon stimulation by inflammatory factors. Activated Thy-1$^+$ fibroblasts secrete transforming growth factor-β (TGF-8), which further enhances HA synthesis through autocrine signaling. The hydrophilic HA absorbs water, leading to extraocular muscle swelling, and promotes differentiation of Thy-1$^+$ cells into myofibroblasts, contributing to inflammation and fibrosis. On the contrary, Thy-1$^-$ fibroblasts differentiate into adipocytes under the induction of T cell-derived lipid-stimulating factors, accompanied by upregulation of TSHR expression. This process is associated with elevated TRAb levels and prolonged disease activity in TAO. The relative balance between these two fibroblast subsets determines whether intraorbital tissues exhibit predominantly adipogenic or fibrotic remodeling [30, 31]. High TRAb levels often indicate that the disease is in the active inflammatory phase rather than having progressed to irreversible fibrosis [32]. In this stage, the mechanical restriction on extraocular muscles is relatively light, and the risk of developing diplopia is low.

Kim et al. [33] retrospectively analyzed the clinical and imaging data of TAO patients to characterize those with diplopia and to explore the association between clinical activity score (CAS) and diplopia. Their findings suggested that CAS may not accurately reflect the degree of extraocular muscle inflammatory activity, as diplopia may continue to progress even in patients with low CAS. Similarly, Nicolì et al. [34] investigated the correlation between TRAb levels and overall clinical outcomes in TAO but found no significant association between TRAb and diplopia. However, neither of these studies integrated clinical and imaging parameters for comprehensive analysis. Given that independent risk factors for diplopia were identified from both clinical and imaging perspectives, this study established a combined clinical-imaging prediction model. The AUC for this joint model reached 0.986, outperforming any single index, showing excellent predictive performance with clear potential for clinical translation.

This study has several limitations. First, as a single-center retrospective study, the sample source was relatively homogeneous, which may have introduced selection bias and limited the generalizability of the findings. Future multicenter prospective studies are warranted to further validate these results. Second, the manual delineation of extraocular muscles and intraorbital tissues on MRI images remain somewhat subjective, despite being independently performed and averaged by two experienced radiologists. The adoption of artificial intelligence-assisted segmentation techniques in future work could enhance measurement objectivity and reproducibility. In addition, this study primarily focused on static morphological parameters and did not incorporate functional MRI parameters, such as extraocular muscle motility, fibrosis degree, perfusion, or diffusion characteristics, which may provide deeper insight into the pathophysiological mechanisms underlying diplopia. Finally, although the combined predictive model demonstrated excellent performance, external validation was not conducted; therefore, its clinical applicability and stability still need to be further evaluated.

Conclusion

MRI enables precise quantitative assessment of intraorbital structural alterations in TAO patients. TRAb and multiple MRI parameters (IR, MR, and LR muscle thickness and EMV) serve as key indicators for predicting the occurrence of diplopia in TAO. The integrated prediction model combining these variables achieved exceptionally high predictive accuracy, providing an objective basis for the early identification of high-risk patients and the optimization of treatment strategies. Furthermore, the positive correlation between diplopia duration and extraocular muscle thickness underscores the close link between symptom severity and structural remodeling. Future research should focus on multicenter validation, longitudinal follow-up, and the integration of functional imaging parameters and molecular biomarkers to advance a precision medicine framework for the early diagnosis, risk assessment, and individualized management of TAO.

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Disclosure of conflict of interest

None.

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References

[1] Du B, Wang Y, Yang M and He W. Clinical features and clinical course of thyroid-associated ophthalmopathy: a case series of 3620 Chinese cases. Eye (Lond) 2021; 35: 2294-2301.

[2] Marinò M, Ionni I, Lanzolla G, Sframeli A, Latrofa F, Rocchi R and Marcocci C. Orbital diseases mimicking Graves' orbitopathy: a long-standing challenge in differential diagnosis. J Endocrinol Invest 2020; 43: 401-411.

[3] Giannuzzi F, Carlà MM, Crincoli E, Gambini G, Hu L, Boselli F, Cuffaro G, Parrilla C, Rigante M, Pagliara MM, Rizzo S and Savino G. Thyroid-related orbitopathy: clinical overview, novel medical treatments and the role of orbital surgery. Int Ophthalmol 2025; 45: 160.

[4] Kahaly GJ, Xi A, Barretto N, Patel H, Qashqai A, Shokoohi M, Spin P and Holt RJ. Teprotumumab improves quality of life in thyroid eye disease: meta-analysis and matching-adjusted indirect comparison. J Endocr Soc 2025; 9: bvaf063.

[5] Smith TJ, Cockerham K, Lelli G, Choudhary C, Taylor S, Barretto N, Enstone A, Oliver L, Lynch J and Holt RJ. Utility assessment of moderate to severe thyroid eye disease health states. JAMA Ophthalmol 2023; 141: 159-166.
[6] Cheng J, Zhang X, Lian J, Piao Z, Zhou L, Gou X, Chen C, Chen L, Jiang K, Cheng J, Ji L and Hong N. Evaluation of activity of Graves' orbitopathy with multiparameter orbital magnetic resonance imaging (MRI). Quant Imaging Med Surg 2023; 13: 3040-3049.
[7] Bartley GB and Gorman CA. Diagnostic criteria for Graves' ophthalmopathy. Am J Ophthalmol 1995; 119: 792-795.
[8] Perros P, Žarković M, Pearce SH, Razvi S, Kolli H and Dickinson AJ. Inter-observer variability of clinical activity score: assessments in patients with thyroid eye disease. Am J Ophthalmol 2023; 252: 94-100.
[9] Liu P, Chen L, Wang QX, Luo B, Su HH, Yuan G, Jiang GH and Zhang J. Histogram analysis of T2 mapping for detecting early involvement of extraocular muscles in patients with thyroid-associated ophthalmopathy. Sci Rep 2020; 10: 19445.
[10] Lee YH, Pineles SL, Ploysangam P and Velez FG. Inferior rectus muscle y-split for thyroid-related vertical strabismus. J Binocul Vis Ocul Motil 2024; 74: 65-68.
[11] Someda SK, Umezawa N, Vaidya A, Kakizaki H and Takahashi Y. Surgical outcomes of bilateral inferior rectus muscle recession for restrictive strabismus secondary to thyroid eye disease. J Clin Med 2023; 12: 6876.
[12] Savino G, Mattei R, Salerni A, Fossataro C and Pafundi PC. Long-term follow-up of surgical treatment of thyroid-associated orbitopathy restrictive strabismus. Front Endocrinol (Lausanne) 2022; 13: 1030422.
[13] Someda SK, Umezawa N, Vaidya A, Kakizaki H and Takahashi Y. Surgical outcomes of bilateral inferior rectus muscle recession for restrictive strabismus secondary to thyroid eye disease. J Clin Med 2023; 12: 6876.
[14] Zheng J, Duan H, You S, Liang B, Chen Y and Huang H. Research progress on the pathogenesis of Graves' ophthalmopathy: based on immunity, noncoding RNA and exosomes. Front Immunol 2022; 13: 952954.
[15] Laurberg P, Berman DC, Pedersen IB, Andersen S and Carlé A. Double vision is a major manifestation in moderate to severe Graves' orbitopathy, but it correlates negatively with inflammatory signs and proptosis. J Clin Endocrinol Metab 2015; 100: 2098-2105.
[16] Shu X, Shao Y, Chen Y, Zeng C, Huang X and Wei R. Immune checkpoints: new insights into the pathogenesis of thyroid eye disease. Front Immunol 2024; 15: 1392956.
[17] Smith TJ. Understanding pathogenesis intersects with effective treatment for thyroid eye disease. J Clin Endocrinol Metab 2022; 107: S13-S26.
[18] Alkhadrawi AM, Lin LY, Langarica SA, Kim K, Ha SK, Lee NG and Do S. Deep-learning based automated segmentation and quantitative volumetric analysis of orbital muscle and fat for diagnosis of thyroid eye disease. Invest Ophthalmol Vis Sci 2024; 65: 6.
[19] Xia D, Zhang H, Wang H, Jiang M, Tang Y, Li Y, Sun J, Song X and Zhou H. Whole-orbit-based multiparametric assessment of disease activity of thyroid eye disease on Dixon MRI. Int Ophthalmol 2024; 44: 213.
[20] Karhanová M, Čivrný J, Kalitová J, Schovánek J, Pašková B, Schreiberová Z and Hübnerová P. Computed tomography and magnetic resonance imaging of the orbit in the diagnosis and treatment of thyroid-associated orbitopathy - experience from practice. a review. Cesk Slov Oftalmol 2023; 79: 283-292.
[21] Rui L, Jing L and Zhenchang W. Diffusion tensor imaging technology to quantitatively assess abnormal changes in patients with thyroid-associated ophthalmopathy. Front Hum Neurosci 2022; 15: 805945.
[22] Zheng J, Duan H, You S, Liang B, Chen Y and Huang H. Research progress on the pathogenesis of Graves' ophthalmopathy: based on immunity, noncoding RNA and exosomes. Front Immunol 2022; 13: 952954.
[23] Koizumi T, Tanaka T, Umeda K, Komiyama D and Obata H. Correlation between extraocular muscle enlargement and thyroid autoantibodies in thyroid eye disease. Jpn J Ophthalmol 2024; 68: 250-258.
[24] Krieger CC, Place RF, Bevilacqua C, Marcus-Samuels B, Abel BS, Skarulis MC, Kahaly GJ, Neumann S and Gershengorn MC. TSH/IGF-1 receptor cross talk in Graves' ophthalmopathy pathogenesis. J Clin Endocrinol Metab 2016; 101: 2340-7.
[25] Fenneman AC, van der Spek AH, Hartstra A, Havik S, Salonen A, de Vos WM, Soeters MR, Saeed P, Nieuwdorp M and Rampanelli E. Intestinal permeability is associated with aggravated inflammation and myofibroblast accumulation in Graves' orbitopathy: the MicroGO study. Front Endocrinol (Lausanne) 2023; 14: 1173481.
[26] Chatzistefanou KI, Brouzas D, Asproudis I, Tsina E, Droutsas KD and Koutsandrea C. Strabismus surgery for diplopia in chronic progressive external ophthalmoplegia. Int Ophthalmol 2019; 39: 213-217.
[27] Karhanová M, Kalitová J, Kovář R, Schovánek J, Karásek D, Čivrný J, Hübnerová P, Mlčák P and Šín M. Ocular hypertension in patients

with active thyroid-associated orbitopathy: a predictor of disease severity, particularly of extraocular muscle enlargement. Graefes Arch Clin Exp Ophthalmol 2022; 260: 3977-3984.
[28] Ugradar S, Parunakian E, Zimmerman E, Malkhasyan E, Raika P, Douglas RN, Kossler AL and Douglas RS. Clinical and radiologic predictors of response to teprotumumab: a 3D volumetric analysis of 35 patients. Ophthalmic Plast Reconstr Surg 2025; 41: 408-414.
[29] Tong X and Shen Q. Identification of immune-related regulatory networks and diagnostic biomarkers in thyroid eye disease. Int Ophthalmol 2024; 44: 38.
[30] Zhang Z, Wu H, Gong X, Yan Y, Li X, Yang R, Wu M and Xu M. A comprehensive epigenetic network can influence the occurrence of thyroid-associated ophthalmopathy by affecting immune and inflammatory response. Sci Rep 2024; 14: 13545.
[31] Ueland HO, Neset MT, Methlie P, Ueland GÅ, Pakdel F and Rødahl E. Molecular biomarkers in thyroid eye disease: a literature review. Ophthalmic Plast Reconstr Surg 2023; 39: S19-S28.
[32] Moledina M, Roos J and Murthy R. Thyrotropin receptor autoantibody assessment in thyroid eye disease: does the assay type matter? Korean J Ophthalmol 2023; 37: 147-156.
[33] Kim JW, Woo YJ and Yoon JS. Is modified clinical activity score an accurate indicator of diplopia progression in Graves' orbitopathy patients? Endocr J 2016; 63: 1133-1140.
[34] Nicolì F, Lanzolla G, Mantuano M, Ionni I, Mazzi B, Leo M, Sframeli A, Posarelli C, Maglionico MN, Figus M, Nardi M, Marcocci C and Marinò M. Correlation between serum anti-TSH receptor autoantibodies (TRAbs) and the clinical feature of Graves' orbitopathy. J Endocrinol Invest 2021; 44: 581-585.