

Clinical profiles of thyroid eye disease with and without strabismus: a comparative study

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Abstract

• **AIM:** To identify differences in clinical features between thyroid eye disease (TED) patients with and without strabismus.

• **METHODS:** This retrospective, single-center, consecutive case series study was conducted on TED patients who were determined to be surgical candidates. The patients' cohort were divided into two groups based on the presence or absence of strabismus. Demographics and complete eye examinations were recorded and compared between the TED and TED with strabismus groups.

• **RESULTS:** A total of 76 patients with TED were enrolled, including 58 males (76.3%) with a mean age of 52.68±10.45y. The 55 patients (male:female=2:1) were found to have TED with strabismus, while the remaining 21 patients (male:female=4:1) had TED without strabismus. There was nearly a four times greater likelihood of lid retraction being associated with TED without strabismus (OR=4.1, $P=0.018$) and they showed higher prevalence of proptosis (95.2%) than the TED strabismus group (63.6%, $P<0.001$). In the TED-strabismus group, 20% of patients had

abnormal head posture (AHP), while none were identified in the TED group ($P=0.029$). Despite the higher incidence of vision-threatening complications such as dysthyroid optic neuropathy (19% vs 8.1%) and exposure keratopathy (4.8% vs 1.8%) in the TED group than in the TED-strabismus group, the difference did not reach statistical significance ($P>0.05$). The most common types of strabismus were hypotropia (36%) and esotropia (29%), respectively.

• **CONCLUSION:** Strabismus-associated TED is characterized by a lower prevalence of proptosis and lid retraction, but a higher incidence of compensatory AHP. Identifying these differences may aid in risk stratification and early intervention for TED patients, particularly those at risk for restrictive strabismus.

• **KEYWORDS:** thyroid eye disease; strabismus; proptosis; lid retraction

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INTRODUCTION

Thyroid eye disease (TED), an autoimmune orbital disorder associated with Graves' disease, manifests with a spectrum of clinical features ranging from mild ocular surface irritation to severe, vision-threatening complications such as dysthyroid optic neuropathy (DON) and restrictive strabismus^[1-2]. While proptosis and eyelid retraction are hallmark signs of TED, the development of strabismus represents a distinct clinical phenotype, arising from fibrotic changes in the extraocular muscles, predominantly inferior and medial rectus muscles^[3-4]. Restrictive strabismus in TED can significantly impair quality of life due to diplopia (17% of patients)^[5] and compensatory abnormal head posture (AHP), necessitating surgical intervention in refractory cases^[6-7].

Emerging evidence suggests that TED patients with strabismus exhibit different clinical and immunological profiles compared to those without ocular motility dysfunction. Prior studies

have proposed a dichotomy in TED subtypes: a fat-dominant phenotype characterized by proptosis and retro-orbital adipose expansion, and a muscle-dominant phenotype marked by restrictive myopathy, fibrosis, and higher rates of strabismus^[8]. However, the precise clinical distinctions between these groups remain incompletely characterized, particularly in cohorts requiring surgical management.

This study compared the clinical features of TED patients with and without strabismus in a surgical referral population, contributing to the growing understanding of phenotypic variation in TED and aiding in early recognition. Clarifying the phenotypic spectrum of TED facilitates earlier identification of patients at elevated risk for strabismus development, enabling more vigilant monitoring and timely intervention. This distinction is important for treatment decisions, as fat-dominant phenotypes often necessitate proptosis-directed interventions; whereas, muscle-predominant cases may benefit from targeted immunomodulation during active disease phases to potentially mitigate fibrotic progression.

PARTICIPANTS AND METHODS

Ethical Approval The research adhered to the Declaration of Helsinki. Approval was obtained from the ethics committee of Tehran University of Medical Sciences prior to conducting the study. The informed consent was waived due to the retrospective nature of this study.

In this retrospective case-series study, we investigated the medical records of 76 TED patients who had been identified as surgical candidates and subsequently referred to Farabi Eye Hospital, Tehran, Iran between 2015 and 2022. Patients were then categorized into two cohorts: those diagnosed with TED accompanied by strabismus ($n=55$), who underwent strabismus surgery at Farabi Eye Hospital, and those with TED, but without concurrent strabismus ($n=21$). The mean age of the patients was 52.68 ± 10.45 y, with an overall male-to-female ratio of 3:1.

The inclusion criteria were: 1) patients aged 18 years or older, 2) patients diagnosed with moderate to severe TED [as defined by the European Group on Graves' Orbitopathy classification, based on the presence of at least two of the following signs^[9]: eyelid retraction ≥ 2 mm, exophthalmos ≥ 3 mm, moderate or severe soft tissue involvement, constant or inconstant diplopia (Gorman score 2–3), or sight-threatening TED (presence of DON or corneal breakdown)]. The diagnosis of TED was made in accordance with the 2014 clinical practice guidelines established by the American Academy of Ophthalmology (AAO)^[10]. The exclusion criteria were: 1) patients with a history of prior strabismus surgery or any other ocular surgeries unrelated to TED, which alter extraocular muscle function and confound the assessment of TED-related strabismus patients, 2) patients with co-existing neurological

or ocular motility disorders (e.g., myasthenia gravis, orbital myositis, cranial nerve palsy), which can independently cause diplopia or strabismus, and obscure TED-specific effects. Additionally, patients with other ocular conditions will also be excluded (e.g., glaucoma, diabetic retinopathy), 3) patients with incomplete medical records or missing key clinical data required for the analysis.

The diagnosis of restrictive strabismus required evidence of limited extraocular motility in one or more gazes based on a motility grading scale. Restriction was defined as limitation of ductions and versions in the field of action of the involved muscle. A positive forced duction test was also required to confirm restriction. In the TED group with strabismus, strabismus surgery was conducted in cases who either had an AHP, or diplopia in primary position accompanied by strabismus larger than 20 prism diopter.

Relevant data was extracted from patient medical records, which included: demographic information (age, gender); smoking history; corrected distance visual acuity (CDVA); refractive error (sphere, cylinder, axis); eyelid examination; slit lamp examination; fundoscopy; Hertel exophthalmometry value; intraocular pressure (IOP); history of medications; deviation test (near and distance prism cover test); and ocular motility assessment (ductions and versions grading).

Statistical Analysis Data was analyzed using SPSS v26 (IBM Corp, Armonk, NY, USA). Normality testing was conducted using the Shapiro-Wilk testing. Fisher's exact test was used to compare categorical variables between the TED and TED-strabismus groups. Continuous variables were analyzed using a *t*-test where the data demonstrated a normal distribution, while the Mann-Whitney test was employed for variables that did not have a normal distribution pattern. *P*-value from Fisher's Exact Test for categorical variables and independent *t*-test for continuous variable. Testing for normality utilized Shapiro-Wilk normality test. Significance correction is $P < 0.05$.

RESULTS

The mean age was 50.00 ± 12.41 y (ranging from 30 to 69 y) in the TED group and 53.71 ± 9.53 y (ranging from 34 to 76 y) in the TED-strabismus group ($P=0.168$). The male-to-female ratio was 2:1 in the TED group and 4:1 in the TED-strabismus group ($P=0.240$). Bilateral involvement was observed in 71.4% of the TED group and 65.5% of the TED-strabismus group ($P=0.786$).

The smoking status was not statistically different between groups ($P=0.478$). Proptosis was observed in 63.6% of TED strabismus group and 95.2% of TED group ($P < 0.001$). Additionally, 47.6% of TED patients had lid retraction; whereas, only 18.2% of TED-strabismus patients exhibited this feature ($P=0.018$). TED patients were found to have a four times higher likelihood of experiencing lid retraction

than TED-strabismus patients [odds ratio (OR)=4.1, 95% confidence interval (CI): 1.36–12.25; $P=0.018$]. The prevalence of lid lag was 4.8% in the TED group, slightly higher than the 3.6% rate observed in the TED-strabismus group; however, this difference did not reach statistical significance ($P=1.000$). Conversely, 5.5% of patients in the TED-strabismus group exhibited lid swelling; while, this feature was absent in the TED group, the intergroup difference was not statistically significant ($P=0.556$).

AHP was observed in 20% of the TED-strabismus group, but none of the TED patients ($P=0.029$). Sight-threatening conditions, such as DON and exposure keratopathy, were observed in 8.1% and 1.8% of TED patients with concurrent strabismus. In the TED group without strabismus, the prevalence of these sight-threatening complications was notably higher, occurring in 19% and 4.8% of cases, respectively, although the difference was not statistically significant ($P=0.251$ and $P=0.479$ for DON and exposure keratopathy, respectively). Comparison of demographic and clinical profile between TED and TED with strabismus group is summarized in Table 1.

There were no statistically significant differences between the two groups regarding CDVA ($P=0.328$, 0.426, for right and left eyes respectively), spherical equivalent ($P=0.972$, 0.733, for right and left eyes, respectively), and IOP ($P=0.086$, 0.807, for right and left eyes respectively; Table 2).

In the TED-strabismus group, the most prevalent subtype of strabismus was hypotropia, occurring in 36% of patients, followed by esotropia in 29% and a combination of hypotropia and esotropia in 18% of patients (Figure 1).

DISCUSSION

The present study offers valuable insights into the distinct clinical characteristics and management approaches observed among patients with TED, with and without concurrent strabismus. Proptosis was the most prevalent sign of orbitopathy in both groups. Patients with TED-related strabismus demonstrated a lower prevalence of lid retraction and proptosis, compared to TED patients without strabismus. Conversely, they experienced a higher incidence of AHP. Given the predominant involvement of the inferior and medial rectus muscles in TED-related strabismus, as indicated by previous studies^[3], our study observed a similar strabismus manifestation, with hypotropia and esotropia being the most prevalent patterns.

A cohort of TED cases, delineated by Rundle’s curve, defined the conventional TED paradigm by progressing from an active inflammatory phase to an inactive phase, followed by fibrotic changes^[11]. However, there are multiple case series highlighting the varying presentations of TED that do not conform to the typical pattern. As described by Iñiguez *et al*^[12], there exists a

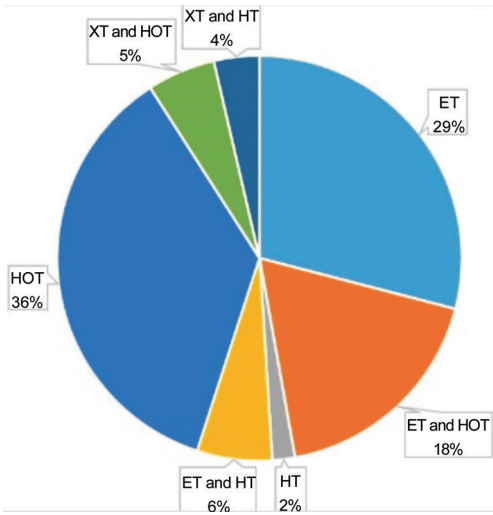


Figure 1 The Percent frequency data for different types of strabismus in thyroid eye disease patients ET: Esotropia; XT: Exotropia; HOT: Hypotropia; HT: Hypertropia.

Table 1 Clinical features of patients with TED with and without strabismus

Parameters	TED (n=21)	TED plus strabismus (n=55)	^a <i>p</i>
Mean age (range), y	50.00±12.41 (30–69)	53.71±9.53 (34–76)	0.168
Smoking	6/9 (66.7%)	19/37 (51.4%)	0.478
Proptosis	20 (95.2%)	35 (63.6%)	<0.001
Laterality			
Unilateral	6 (28.6%)	19 (34.5%)	0.786
Bilateral	15 (71.4%)	36 (65.5%)	
Lids			
Normal	10 (47.6%)	40 (72.7%)	0.013
Swelling	0 (0.0%)	3 (5.5%)	0.556
Lag	1 (4.8%)	2 (3.6%)	1.000
Retraction	10 (47.6%)	10 (18.2%)	0.018
AHP	0	11 (20.0%)	0.029
Diplopia	4 (19%)	32 (58.2%)	0.249
Corneal involvement			
Normal	17 (81%)	50 (90.9%)	0.251
PEE	2 (9.5%)	4 (7.3%)	0.666
Exposure keratopathy	1 (4.8%)	1 (1.8%)	0.479
Optic nerve			
Normal	17 (81%)	50 (90.9%)	0.449
DON	4 (19%)	5 (9.1%)	0.251

TED: Thyroid eye disease; AHP: Abnormal head posture; PEE: Punctate epithelial erosion; DON: Dysthyroid optic neuropathy.

distinct subgroup of TED patients who exhibit a predominance of fibrotic and restrictive changes, in contrast to the hallmark proptosis of the more common TED phenotype. Notably, this subgroup lacks the clinically apparent inflammatory features that typically characterize the disease course yet still experiences a progressive clinical presentation. Gerlach *et al*^[13] have documented a series of seven cases of TED characterized

Table 2 Comparison of visual acuity, refraction, IOP and angle of deviation between the two study groups

Parameters	Groups	Number	Minimum	Maximum	Mean±SD	<i>P</i>
CDVA (logMAR)						
Right eye	TED	21	0.00	0.40	0.06±0.10	0.328 ^a
	TED+Strabismus	55	0.00	0.70	0.09±0.14	
Left eye	TED	21	0.00	0.70	0.09±0.18	0.426 ^a
	TED+Strabismus	55	0.00	2.00	0.17±0.33	
Spherical equivalent						
Right eye	TED	21	-3.00	3.00	0.11±1.41	0.972 ^a
	TED+Strabismus	55	-4.00	25.00	0.41±3.57	
Left eye	TED	21	-2.00	2.25	-0.10±1.11	0.733 ^a
	TED+Strabismus	55	-8.00	8.00	0.06±1.81	
IOP (mm Hg)						
Right eye	TED	21	13	32	18.88±4.70	0.086 ^a
	TED+Strabismus	55	14	30	19.24±4.38	
Left eye	TED	21	10	25	16.37±3.28	0.807 ^b
	TED+Strabismus	55	10	25	16.37±2.94	
Angle of deviation (prism diopter)						
Horizontal						
Near	TED+Strabismus	55	0	95	17.07±20.30	0.030 ^c
Distance	TED+Strabismus	55	0	95	17.98±21.30	
Vertical						
Near	TED+Strabismus	55	0	50	18.10±14.61	0.028 ^c
Distance	TED+Strabismus	55	0	50	18.27±14.69	

TED: Thyroid eye disease; CDVA: Corrected distance visual acuity; IOP: Intraocular pressure. ^aMann-Whitney *U* test; ^bStudent's *t* test; ^cPaired *t*-test. Testing for normality utilized Shapiro-Wilk normality test. Significance correction is *P*<0.05.

by pure muscle involvement, where proptosis was neither present at the onset nor developed during the course of the disease. These observations underscore the variability in TED presentations, suggesting distinct pathogenic mechanisms and the need for tailored treatment approaches.

Our findings align with the observations from the study by Choi *et al*^[14], who investigated distinct clinical features of 24 TED patients with strabismus and 15 without strabismus. They found that patients with TED accompanied by strabismus were older and exhibited significantly less proptosis in Hertel exophthalmometry, and a higher prevalence of extraocular muscle enlargement compared to those without strabismus. Additionally, levels of thyroid-stimulating hormone receptor antibodies (TRAb) were markedly elevated in the strabismus group, indicating distinct immunopathophysiological mechanisms between the two groups^[14]. The unique clinical profiles of patients with TED have been investigated in various research projects. These investigations have characterized TED patients based on the predominant increase in fat versus muscle volume (MV), as assessed through volumetric analysis using magnetic resonance imaging (MRI) or computed tomography (CT) scans. Patients with a muscle volume-dominant phenotype, defined by MV/orbit volume (OV) ratio

exceeding the 97.5 percentile, were found to be older, had higher levels of TRAb, and associated with higher clinical activity scores. Additionally, this subgroup displayed more pronounced diplopia and greater impairment of eye muscle contractions without significant inflammatory involvement of the orbital connective tissue. In contrast, patients with a fat volume (FV)-dominant disease, indicated by FV/OV ratio greater than the 97.5 percentile of age-specific reference intervals, exhibited more significant proptosis, had milder inflammation (lower clinical activity scores), and typically presented later in the disease course more than one-year duration), but had a lower occurrence of DON^[8,13,15]. In fat-dominant TED, orbital fibroblasts differentiate into adipocytes under the influence of thyroid-stimulating hormone receptor (TSHR) and insulin-like growth factor-1 receptor (IGF-1R) autoantibodies, leading to retro-orbital fat expansion^[16]. TED-related strabismus is characterized by fibroblast differentiation into myofibroblasts, driven by thyroid-stimulating immunoglobulins (TSI) and anti-calnexin 1 (anti-CASQ1) or anti-collagen XIII (anti-COLXIII) autoantibodies, which target extraocular muscle fibers and orbital fibroblasts, respectively^[17]. These differences underscore the need for tailored diagnostic and therapeutic approaches, as fat-dominant TED may require

orbital decompression for proptosis, while muscle-dominant cases often need immunosuppression or strabismus surgery to address restrictive fibrosis and optic neuropathy^[18-20].

Proptosis is primarily associated with retro-orbital fat swelling rather than as a direct consequence of extraocular muscle involvement in TED, and thus would be expected to have a less direct association with TED-related myopathy and the restrictive pattern. Eyelid retraction is a hallmark feature of TED and arises from multiple mechanisms, including sympathetic overstimulation of Müller's muscle due to thyroid hormone excess in early inflammatory stages^[21], mechanical effects of orbital fat expansion and proptosis pushing the eyelid forward^[22], or fibrosis and contracture of the levator palpebrae superioris muscle^[23]. Our findings indicated that lid retraction was significantly higher in patients without strabismus than the other group, likely due to the higher prevalence of proptosis observed in this subgroup. In contrast, TED patients with strabismus tend to exhibit normal eyelid positioning. The mechanical effects of orbital fat expansion and anterior displacement stretch the levator palpebrae complex, contributing to the higher incidence of lid retraction in TED patients without strabismus. Although fibrosis of the levator palpebrae can lead to lid retraction in late fibrotic stages, muscle-dominant TED primarily involves fibrosis of the extraocular muscles rather than the levator. Chronic muscle fibrosis results in atrophy and shrinkage, reducing orbital crowding. Additionally, late-stage TED often coincides with euthyroidism, diminishing sympathetic overdrive on Müller's muscle. In our study, the higher prevalence of lid retraction in TED patients without strabismus appears attributable to increased proptosis in this subgroup. However, the lack of data on disease duration, activity, and thyroid hormone levels limits further confirmation of these findings.

In our study, the significantly higher prevalence of AHP in TED patients with strabismus compared to those without can be attributed to compensatory mechanisms for maintaining binocular vision^[24].

Although we did not find statistically significant differences in the prevalence of DON between the two subtypes, the lack of significance may reflect limited power due to small subgroup sizes rather than a true absence of association. While larger studies reported a higher prevalence of DON in the muscle-dominant TED, attributing it to the compression of the optic nerve by the enlarged extraocular muscles, notably at the apex. They proposed that isolated retro-orbital fat swelling and stretching forces without concurrent muscle enlargement may not substantially contribute to the development of neuropathy^[25-26].

While previous work by Nunery *et al*^[27] has illustrated a significant association between smoking and the development

of restrictive myopathy in patients with TED, the present study did not yield similar results. The male predominance in our cohort contrasts with population-level TED data but mirrors surgical series, where males often present with advanced disease^[19]. This suggests our findings may generalize best to severe, muscle-dominant TED requiring intervention.

The present study is not without limitations. The retrospective design, modest sample size, and single-centre patient inclusion represent potential constraints that should be acknowledged. Further prospective, multicenter studies with larger cohorts are warranted to validate findings and better characterize factors predicting risk for developing strabismus in TED. While disease duration and progression from inflammatory to fibrotic stages may influence the development of strabismus in TED, our retrospective study design did not capture this temporal data, preventing analysis of how chronicity affects clinical presentations between groups. The male predominance in our study may reflect referral bias toward severe TED in males, which limits the generalizability of our findings. Regional genetic or environmental factors could also contribute, warranting validation in gender-balanced cohorts. Our study exclusively included surgical cohorts which warrants further prospective studies that encompass mild to moderate TED managed medically to validate whether our observed phenotypic distinctions extend across the entire disease spectrum. Further prospective studies incorporating autoantibody profiling and advanced orbital imaging are needed to refine predictive models and optimize therapeutic strategies. Additionally, these studies should investigate whether early immunomodulatory or anti-fibrotic interventions alter the trajectory of ocular motility dysfunction, providing evidence-based guidance for timely and targeted management. In conclusion, our study highlights distinct clinical phenotypes in TED patients with and without strabismus, underscoring that strabismus-associated TED exhibits less proptosis and lid retraction, but a higher prevalence of AHP, likely due to restrictive extraocular muscle fibrosis. These findings support the growing recognition of TED subtypes, fat-dominant versus muscle-dominant, with differing pathophysiological mechanisms and clinical trajectories. Identifying these differences may aid in risk stratification, early intervention, and tailored management for TED patients, particularly those at risk for restrictive strabismus.

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