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Ocular Surface Disease in Thyroid Eye Disease: A Narrative Review

Harkaran S. Rana, DO[1], **Sruti S. Akella, MD**[2], **Carson E. Clabeaux, DO**[3], **Zachary P. Skurski, DO**[4], **Vinay K. Aakalu, MD, MPH**[2]

[1]Department of Ophthalmology, Walter Reed National Military Medical Center, Bethesda, Maryland, United States

[2]Department of Ophthalmology and Visual Sciences, University of Illinois-Chicago, Chicago, Illinois, United States

[3]Department of Ophthalmology, Madigan Army Medical Center, Tacoma, Washington, United States

[4]Department of Ophthalmology, Keller Army Community Hospital, West Point, New York, United States

Narrative Abstract:

Ocular surface disease (OSD) in the setting of thyroid eye disease (TED) is traditionally thought of as a natural consequence of anatomical changes such as proptosis and corneal exposure. However, a growing body of research suggests that ocular surface inflammation and multi-factorial changes to the homeostasis of the ocular surface contribute substantially to the OSD seen in TED patients. In this paper we review the existing literature which highlights the work and existing theories underlying this new paradigm shift.

Keywords

dry eye; ocular surface disease; thyroid eye disease; exposure keratopathy

1.1 Introduction

In 1835 Robert Graves first described the clinical triad of systemic hyperthyroidism, goiter, and exophthalmos [1]. The exophthalmos he described has since been recognized as one manifestation of what we now call thyroid-associated ophthalmopathy (TAO) or thyroid eye disease (TED), which can occur in patients who are hypo-, hyper-, or even eu-thyroid.

Corresponding Author: Vinay Aakalu, MD, Department of Ophthalmology and Visual Sciences, 1855 West Taylor Street, Suite 3.158, Chicago, Illinois 60612, vaakalu@uic.edu.

In the decades since Dr. Graves' first description, it has become clear that TED causes more manifestations than exophthalmos. In fact, one of the most frequently reported symptoms is ocular pain, which is generally attributed to ocular surface disease (OSD) [2]. OSD has been shown to negatively impact patients' functionality as well as quality of life; conversely, successful treatment of OSD has been shown to enhance long-term patient outcomes [3]. Unfortunately, TED and the associated OSD are often challenging for physicians to manage [3-6]. Rather than just exposure keratopathy related to exophthalmos and lid retraction, evidence has emerged pointing to an inflammatory cause of TED-related OSD. This review aims to synthesize and summarize the most recent literature regarding the ocular surface manifestations of TED, which may help guide management.

2.1 Methods

The authors searched PubMed, Embase, and Google Scholar databases using the terms "Graves' ophthalmopathy", "thyroid associated ophthalmopathy", "ocular surface AND Graves'", "ocular surface AND thyroid eye disease", "dry eye AND thyroid eye disease", "inflammation AND Graves' disease", "meibomian gland AND Graves' disease", "thyroid eye disease", "thyroid eye disease AND cornea", "Graves disease AND ophthalmology", "Graves disease ocular manifestations", "Graves disease AND treatment"", "thyroid eye disease AND treatment", "Graves disease AND management", "thyroid eye disease AND management", "Graves disease AND tear" "thyroid eye disease AND tear", "Graves disease AND immunology", "Graves disease AND pathophysiology", "thyroid eye disease AND updates", "Graves disease AND updates", "Graves disease AND dry eye", "dry eye in thyroid eye disease", "corneal findings AND Graves", "corneal changes AND Graves", "ocular surface disease AND Graves", "Graves AND diagnosis", and "inflammation AND Graves".

A total of 82 articles, published from 1835 to 2021 in the English language or with English translations, were included. Articles published earlier than 2010 this timeframe were cited for foundational knowledge on the topic.

3.1 Epidemiology

The prevalence of OSD amongst TED patients is estimated to range between 65-95% [7-10]. Conversely, a 2019 population-based study of comorbidities in patients with dry eye disease showed that 24.7% of patients with chronic dry eye disease also had some form of systemic thyroid disease [11]. Estimates of OSD within TED vary: although Bartley found this to occur at a rate of approximately 30%, later studies done by Ismailova *et al.* and Achtsidis *et al.* noted a much higher incidence of dry eye syndrome, roughly 65-68%, utilizing the international dry eye working group (DEWG) criteria [2, 7, 12].

In one study by Kashkouli *et al.*, incidence of dry eye disease (DED) was found to vary considerably depending on whether DED was defined as subjective, objective, or definite [13]. Subjective disease, defined as an ocular surface disease index (OSDI) score greater than or equal to 13, had an incidence of 77%; objective disease, defined as the presence of one exam finding (accelerated tear breakup time, positive Schirmer testing, high tear

osmolarity, or fluorescein staining) had an incidence of 89.2%, which is somewhat higher than the estimated incidence of these findings in the literature [13]. For instance, tear break up time ranges from 31%-85%, aqueous deficiency from 19%- 39.2%, meibomian gland disease from 48%-56.8%, and increased tear osmolarity is estimated to be approximately 16.2% [13, 14, 15]. Finally, definite DED, defined as the presence of both subjective and objective disease, occurred at a rate of 67.7%.

Within the OSD positive subset of TED patients, relatively little epidemiological data exists; however, the most recent studies suggest that the average age and gender predilection is similar to the rates found among all TED patients. Among 119 patients with TED and features of dry eye disease, Park *et al.* found an average age of 45.8 years and a predilection for females (69.4%) [9]. Lo *et al.* found a similarly high rate of OSD among female TED patients: 80.7% of their 88 patients were female [16]. This is consistent with prior studies showing a female predilection for generalized thyroid eye disease [17, 18].

4.1 Pathogenesis

The pathogenesis of OSD arising from TED is multi-factorial: first, there are structural changes from expansion and differentiation of orbital fibroblasts, resulting in proptosis and changes in eyelid position which can lead to increased ocular surface exposure, altered blink dynamics, and ultimately evaporative dry eye disease. Simultaneously, tear-film changes and ocular surface expression of pro-inflammatory cytokines also play a role [7, 19-24].

Overexpression of pro-inflammatory cytokines are associated with changes in ocular surface homeostasis among TED patients and inflammatory DED. Researchers have identified increased levels of IL-1β, IL-6, IL-8, IL-10, IL-17A, and TNF-α in known euthyroid patients with moderate-to-severe TED [25, 26]. Some cytokines have been more extensively studied than others. For example, Fang *et al.* found that in blood samples of euthyroid patients, the number of $CCR6^+$ IL-17A-producing T cells was higher with active TED and correlated positively with the clinical activity score (CAS), the gold-standard measurement tool for inflammatory activity in TED. With lower CAS levels, the number of these cells declined [27].

IL-8 has also been implicated in the inflammatory cascade leading to ocular surface disease [25-29]. Rotondi *et al.* found that serum IL-8 is elevated in untreated TED, but levels return to normal with successful systemic treatment of methimazole when compared to healthy controls [30]. They also found that IL-8 tends to be elevated in hyperthyroid TED compared to healthy controls, but that there was no difference between euthryoid TED patients and controls [30]. Douglas *et al.* similarly suggested that the fibrocyte-mediated production of IL-8 may be used as a marker for disease activity [23].

In general, pro-inflammatory cytokines within the tear-film may be associated with decreased tear production within the lacrimal gland (IL-β, IL-6), increased leukocyte migration into the avascular corneal tissue (IL-8) as well as activation of the MAPK pathway leading to mucin disruption, apoptosis, and goblet cell loss within the ocular surface [25]. This decrease in tear production relates directly with aqueous tear-deficient DED.

5.1 Clinical Presentation

Patients with OSD in the setting of thyroid eye disease typically present with one of the following: foreign body sensation, blurred vision, dryness, or conjunctival injection, at an estimated prevalence of 65-95% [7-10, 13]. Kashkouli *et al.* found that most patients (89.4%, n=271) with TED have bilateral disease [31]. Compared to those patients with unilateral disease, a bilateral presentation tends to be associated with older age, more severe disease, and higher activity scores. However, asymmetric presentation between the two eyes is not uncommon. [31].

Although numerous systems exist to grade severity and disease activity of generalized thyroid eye disease, including the clinical activity score (CAS) and European Group on Graves' Orbitopathy (EUGOGO) [32-34], none of these grading systems directly assesses the severity of dry eye disease. Perhaps the most useful assessment is the ocular surface disease index (OSDI), which has been shown to be significantly increased in active TED patients compared to inactive TED patients as well as healthy controls [35]. However, the CAS has also been shown to be a significant predictor of severe OSDI early on the course of thyroid-associated dry eye disease: Lo *et al.* found that every increase in CAS of one doubled the risk of severe OSDI [16]. Another recent study suggests that Meibomian gland dropout is greater in patients with a higher CAS and OSDI results [36].

Some authors suggest that inflammatory dry eye may actually be an early manifestation of TED. In a single-center study of patients presenting with refractory DES, 21 of 539 patients were found to have occult TED, diagnosed by orbital echography. All of the patients responded to treatment with cyclosporine with or without steroids. None of the patients studied had exophthalmos or typical findings of TED, although half were noted to have subtle widening of palpebral fissure [14].

6.1 Diagnosis

Although studies have described the prevalence of dry eye disease within TED, very few of these studies distinguish between objective, subjective, or definitive OSD. Clinical evaluation focused on determining whether TED patients have OSD should thus first begin with an attempt to characterize the patient's disease into one of these categories.

6.1.1 Subjective Disease

A thorough review of symptoms is a crucial first step in assessing the ocular surface. Questionnaires such as the validated OSDI survey can be helpful [37]. The OSDI is a twelve-point questionnaire directed at symptoms, limitations of activities of daily living, and relation of symptoms to inciting factors. One study of 50 eyes in patients with newly diagnosed Graves' disease found that the OSDI score in this population was higher than healthy controls [21]. The OSDI may also correlate with CAS: Lo *et al.* observed patients with TED who suffered from symptomatic surface disease within the first 9 months following diagnosis and found that the CAS had a higher direct correlation with the ocular surface disease index (OSDI). For patients whose symptoms persisted past nine months, the

degree of punctate epithelial erosions (PEE) was a more predictive factor for a worse OSDI score [16].

6.1.2 Objective Disease

Prior to a clinical examination, serologies may be useful in understanding whether the patient is in the active or inflammatory phase of disease. There is a strong association between thyroid stimulating immunoglobulins (TSI) and TED. Lytton *et al.* found that all hyperthyroid Graves' disease patients and TED patients were TSI positive. Additionally, based on the CAS, this study concluded that there was a strong correlation between disease severity and TSI levels [38].

A careful external examination should then be performed. Vertical and horizontal palpebral fissure, eyelid retraction, inferior and superior scleral show, and degree of lagophthalmos are assessed. Proptosis, or exophthalmos, is measured with a Hertel exophthalmometer. The conjunctiva should be examined for injection, especially over the extraocular muscle insertions and the superior bulbar conjunctiva, which may show signs of superior limbic keratoconjunctivitis (SLK). Often bilateral and asymmetric, SLK may present with redundant injected superior conjunctiva that classically stains well with rose Bengal dye [28, 39, 40].

Examination of the cornea should generally include staining with fluorescein, lissamine green, or rose Bengal to assess for signs of superficial keratopathy. In severe cases, filaments may be present. Corneal sensation should also be measured prior to instillation of any topical anesthetic drops, as it has been shown to be reduced in patients with TED and have a positive correlation with presence of OSD [12]. Finally, recent technologic advancements have led to the development of several laboratory assays which specifically assess the health and viability of the ocular surface; these will be discussed in greater detail below.

6.1.2.1 Tear-film stability, composition and osmolarity—Assessing the health of the tear film is fundamental to understanding surface disease. One easily performed test is tear breakup time, done by instilling fluorescein and monitoring for the development of dark spots under a cobalt blue filter. Tear breakup time (TBUT) less than 10 seconds is considered a positive test [41]. More objective assays have been developed including direct assessment of the tear-film evaporative rate (TER) or TBUT. One example is the VapoMeter which is a closed chamber device that utilizes changes in humidity and temperature to gauge the evaporative rate [15]. In a small cohort of 20 patients, Abusharaha *et al.* confirmed that patients with thyroid eye disease had an appreciable increase in their TER. These findings had an inverse correlation with the OSDI [42].

Schirmer testing is another modality that can be performed, with measurements <10mm at 5 minutes and positive staining of the ocular surface indicating pathology. However, the utility of the Schirmer test has been frequently questioned due to the high variations seen when monitoring different stages of surface disease. It has not been shown to be reliable in mild-to-moderate disease [43].

Other non-invasive testing includes measurement of tear-film osmolarity, measured in mOsm/L. A threshold value of 308 moSm/L measured on the TearLab™ Osmolarity System has shown a 75% and 95% sensitivity in diagnosis mild/moderate and severe DED respectively [44]. Hyperosmolarity can lead to multiple changes in ocular surface physiology including decreased goblet cell density, decreased granulocyte survival rate, and morphological cell changes [45-48]. Sullivan *et al.* in a prospective multi-center study found tear osmolarity to have the highest correlation coefficient to dry eye disease severity; this relationship was assessed using the OSDI. Expanding on the previous study, in 2012 Sullivan *et al.* performed a longitudinal case series study and found that tear osmolarity had the least amount of variability when compared with other physical features of dry eye disease (DED), including corneal and conjunctival staining, TBUT and meibomian gland grading. Both studies also showed that higher tear osmolarity is associated with a higher OSDI score [44, 49].

6.1.2.2 Lipid Layer—In the past decade, meibomian gland (MG) architecture and function have become an important part of the complete evaluation of a patient with evaporative DED. In 2015, Kim *et al.* compared 51 patients with TED to 31 control patients without TED [50]. In this study they utilized non-contact meibography (meibo-score) to visualize the MG architecture. A higher meibo-score is associated with obstructive MGD and was found to have a higher prevalence in patients with TED. Additionally, a statistically significant positive correlation was seen between the meibo-score and exophthalmos, TBUT, and palpebral fissure height [40, 51].

Several authors have found increased meibomian gland dropout, particularly in the central region of the upper eyelid, in TED patients. In a study by Wang *et al.*, patients with active TED had worse meibomian gland disease (MGD) and thicker lipid layers than patients with inactive TED [52]. Overall, unfavorable changes to the lipid layer appears to contribute significantly to OSD [42,53].

6.1.2.3 Corneal Biomechanics—Confocal microscopy is a growing field of study in regards to the ocular surface disease in TED and has served to confirm a pro-inflammatory disease model. Villani *et al.* reported that patients with TED have a reduction in epithelial cellular density, an increase in stromal keratocyte activity, and a reduction in the number of corneal nerves compared to healthy corneas [54, 55]. This phenomenon is thought to be the result of increased IL-6 and IL-1 cytokines which have the ability to induce nerve growth factor allowing for proliferation in stromal cell density and activated keratocytes [54]. Meanwhile, Wu *et al.* found a positive correlation between central corneal Langerhans cell activity and patients' CAS and OSDI scores [56].

Differences in the corneal biomechanical properties in patients with TED have also been identified using an ocular response analyzer (ORA) [57]. The ORA provides two corneal parameters in relation to corneal structure: corneal hysteresis (CH), which serves as an indicator of the viscoelastic mechanical damping ability of the cornea; and corneal resistance factor (CRF), an indicator of total elastic resistance. CH was found to be significantly lower in TED patients. CRF was similarly lower in TED patients although this was not statistically significant [57]. Changes in the CH are thought to be related to

microstructural changes in the stroma of the cornea, the arrangement of collagen thin strips and increased amount of activated keratocytes [25, 53, 57, 58]. Interestingly, lower CH may also be a cause of higher average intraocular pressures (IOP) among TED patients [57, 59].

6.1.2.4 Inflammatory Markers—Many inflammatory markers have been found in the tears of patients with TED, and specific markers can be found in variable quantities in different stages of the disease. For instance, Kim *et al.* measured blood serum concentrations of IL-17, IL-6, IL-16, IL-23 in both active and inactive TED population and determined that the pro-inflammatory markers of IL-17 may have a role in active TED [60]. Additionally, IL-1b, IL-6, TNF-alpha, and IL-8 concentrations have been shown to be elevated in active TED compared to health controls. Huang and colleagues found a positive correlation between CAS and proinflammatory interleukins (IL-1b, IL-6, and IL-8) within the tears, suggesting the role of these cytokines as potential markers for disease activity [25, 26, 61, 62].

Conversely, studies have shown that healthy controls have higher levels of anti-inflammatory cytokines in tears and serum compared with their TED counterparts. Specifically, IL-10 and IL-1 alpha have been shown to be elevated in euthyroid patients. IL-10 decreases inflammatory cytokines by downregulating ICAM-1 and inhibiting the expression of IL-6 and TNF-alpha [61, 63-67]. While individual cytokines are often elevated, studies recommend comparing the ratio to evaluate the net effect of inflammatory cytokines to anti-inflammatory to characterize disease activity. Given the knowledge of significant differences in these ratios, future disease monitoring may be targeted to comparing pro- and anti-inflammatory cytokine ratios in tears, as this testing has been proven to determine current ocular surface involvement within TED populations [61].

Finally, increased levels of reactive oxygen species (ROS) may be implicated in the pathogenesis of ocular surface disease [68]. Choi *et al.* investigated the concentrations of oxidative stress markers in the tears, discovering that 8-hydroxy-2'-deoxyquanosine (8-OHdG) and malondiadehyde (MDA) were increased in patients with active TED. They also found that these increases had a strong correlation with CAS [69]. These studies conclude that oxidative stress markers could be followed as biomarkers for active and inactive disease; furthermore, treatment with antioxidants may also be a future option in the management of TED, as suggested by Marcocci *et al.* and their work with the antioxidant selenium [69, 70].

6.1.3 Definite Disease

Many of the previous studies regarding surface disease in thyroid patients have focused on either subjective or objective markers [7, 9,12, 13, 21, 25, 26, 50, 52-54, 56, 71]. However, as further work is done in this academic area, it will be of greater value to adhere to the most recent, standardized definition of DED as outlined in the International Dry Eye Workshop (DEWS) II [22]. For example, Kashkouli *et al.* defined definite disease as a patient experiencing at least one of each subjective and objective criteria. In their study they used the definition of DED from DEWS II to assess the frequency of disease [13].

7.1 Management

Management of OSD-TED can be challenging, as lid abnormalities causing exposure keratopathy need to be addressed in tandem with addressing inflammatory activity at the ocular surface. The following sections discuss various treatment options, organized from least to most invasive.

7.1.1 Topical Treatment

Mild ocular surface disease in TED may be managed with artificial tears, ointments, and nighttime moisture chambers. This approach helps to combat the detrimental effects of exposure keratopathy and hyperosmolarity of the tear-film [32, 72]. Consideration could be given to use preservative-free artificial tears four times a day while awake, with increasing frequency up to hourly as needed. Ointment may also be added nightly and, in more severe cases with lagophthalmos, moisture chamber goggles may be helpful overnight. When artificial tears fail to provide relief or where tear osmolarity studies reveal a significant inflammatory component, the long-term addition of topical cyclosporine emulsion 0.05% applied two times per day can be considered [32, 73].

A short course of topical steroids can also be considered in patients with contraindications to systemic steroids, but patients should be counseled on the potential for intraocular pressure spikes and cataract formation. Additionally, topical steroids should be used cautiously in patients with severe keratitis due to the delayed epithelial healing [74-76]. Use of Prosthetic Replacement of the Ocular Surface Ecosystem (PROSE) and other therapeutic contact lenses are an emerging adjunctive treatment for some of the ocular surface manifestations of TED [77-79]. The treatments discussed in this section are appropriate for all three types of DED (evaporative, aqueous deficient, and mixed disease).

7.1.2 Systemic Treatment

Systemic therapies given for general TED management may have beneficial effects on TED associated OSD. Interestingly, intravenous steroids used to treat moderate to severe TED have also been shown to affect OSD: Xu *et al.* conducted a study showing a statistically significant reduction in the ocular surface disease index (OSDI) and significant reduction in inflammatory mediators of the tear film after 12 weeks of methylprednisolone therapy [26]. If systemic steroids are used, a meta-analysis by Gao *et al.* found that intravenous administration was superior to oral steroids in lowering the CAS [80]. Meanwhile, Mu *et al.* investigated treatment response in 90 patients with active moderate-severe TED over a 12-week period who were randomized between daily and weekly intravenous (IV) steroids. Their study found that daily steroid dosing resulted in a lower CAS score than patients receiving weekly steroids; however, serum cytokine levels yielded similar results [8].

Finally, the recent FDA approval of teprotumumab infusions to treat moderate to severe thyroid eye disease has expanded the treatment options available to patients with active, moderate-severe TED [71, 81]. Although there is currently no data available on ocular surface disease after treatment with teprotumumab, this will be an area of interest going forward.

7.1.3 Surgical Treatment

Surgical intervention for the OSD manifestations of mild TED are of particular use in combating the evaporative form of DED. Treatment may consist of early punctal occlusion with temporary punctal plugs; in refractory cases, some patients may elect for cauterization or destruction of their puncta [77]. As the patient progresses to sight-threatening TED, further surgical intervention may become necessary to address exophthalmos and lagophthalmos. Depending on the severity of lid malposition and degree of exposure, options include a temporary or permanent tarsorrhaphy; levator recession; or surgical decompression with or without subsequent repair of upper or lower eyelid retraction. In advanced disease where exposure has led to corneal degeneration and ulceration, amniotic membrane grafting can be performed with or without tarsorrhaphy to prevent progression and perforation while other topical or systemic treatments are allowed to take effect [34, 82].

8.1 Conclusion

Ocular surface disease in TED is a complex process that extends well beyond proptosis and exposure keratopathy. To adequately treat OSD, initial characterization of the patient's disease activity and severity is important. Following this, a step-wise approach can be utilized ranging from conservative management to surgical intervention combined with topical or systemic therapy. This review highlights the emergence of a truly multifactorial model of ocular surface disease, one that requires an understanding of ocular inflammation. As further studies are performed, it is likely that physicians will be able to provide a targeted treatment approach specific to elevated inflammatory biomarkers.

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Table 1.

Summary of the most relevant articles on ocular surface disease and thyroid eye disease within the past decade (2010-present).

ARTICLE (YEAR)	NUMBER OF PATIENTS/ EYES*	STUDY DESIGN	TYPE OF OSD	TYPE OF TED	MEAN CAS	MEAN OSDI	MEAN TBUT AND/OR % ABNORMAL	MEAN SCHIRMER (MM)	MEAN TEAR OSMOLARITY	MEIBOSCORE AND/OR % WITH MGD	% WITH SURFACE STAINING	EYELID/ GLOBE DYSFUNCTION
PARK & BAEK (2019)[9]	98/NR	Prospective, Observational	Ev	Active (20.4%) & inactive thyroid eye disease [b, c]	1.88+/− 1.5	NR	4.1 +/− 1.9	8.3 +/− 2.0	NR	1.21 +/− 0.76 (upper lid) 0.8 +/− 0.82 (lower lid)	*author specified score*	Ex: 17.4 +/− 2.7
KASHKOULI (2018)[13]	38/74	Prospective, Observational	Ev, Aq	Moderate to severe [a]	1.4+/− 1.03	27.1	7.9+/− 3.6	13.03 +/− 8.9	295.9+/− 19.4 (mOsm/L)	NR & 56.8%	35.1%	Ex: 21.4+/− 2.5
BRUSCOLINI (2014)[21]	25/50	Prospective, Observational	Ev, Aq	Non-exophthalmic Graves' [c]	none	22.7 +/− 16.3	6.7 +/− 2.9	8.2 +/− 4.9	NR	NR	*author specified score*	none
KIM (2015)[50]	51/51	Retrospective, Observational	Ev	Graves' Ophthalmopathy [c]; Active & inactive [b]	2.31+/− 1.59	25.65 +/− 14.43	5.53 +/− 2.55 & NR	NR	NR	1.67 +/−1.58	NR	NR
WANG (2018)[52]	17/31	Prospective, Observational	Ev	TED [c]; Active & inactive	1.6 +/− 0.7	NR	NR	Total TED group: 12.6+/− 9.0 Active group: 9.2 +1− 5.6 Inactive group: 14.5 +/− 10..0	NR	NR & 87.1%	NR	Total TED group Ex 20.4+/− 5.3 Active group Ex: 23.1+/− 4.3 Inactive group Ex:18.5 +/− 3.3
INOUE (2020)[53]	19/38	Prospective, Observational	Ev	Graves' Ophthalmopathy [c]; Active & Inactive [b]	NR	NR	4.7 +/− 3.2	10.5 +/− 8.8	NR	1.0 +/− 0.6 (upper lid) 0.9 +/− 0.6 (lower lid)	NR	Ex: 18.8+/− 1.8 Palpebral fissure height >7mm: 91.7% Eyelid swelling: 57.9%.
VILLANI (2010)[54]	26/52	Prospective, Observational	NR	Graves' Orbitopathy [a]; Active & Inactive [b]	Active: 3.72 +/− 0.90 Inactive: 0.93 +/− 0.79	Active: 29.13 +/− 12.48 Inactive: 22.01 +/− 17.39	Active: 6.64 +/− 2.23 Inactive: 6.45 +/− 3.07	Active: 9.84 +/− 2.96 Inactive: 9.54+/− 2.91	NR	NR	NR	NR
SMITH (2017)[71]	88/ 176**	Prospective, Interventional	NR	Active thyroid associated	Pre-teprotumumab:	NR	NR	NR	NR	NR	NR	Pre-treatment Exoph : 23.4 +/−

ARTICLE (YEAR)	NUMBER OF PATIENTS/ EYES*	STUDY DESIGN	TYPE OF OSD	TYPE OF TED	MEAN CAS	MEAN OSDI	MEAN TBUT AND/OR % ABNORMAL	MEAN SCHIRMER (MM)	MEAN TEAR OSMOLARITY	MEIBOSCORE AND/OR % WITH MGD	% WITH SURFACE STAINING	EYELID/ GLOBE DYSFUNCTION
				ophthalmopathy *b*	5.1 +/− 0.97 Post-teprotumumab: −3.43 +/− 0.18							3.2 After Teprotumumab: −2.46 +/− 0.20
ISMAILOVA (2013)[7]	46/92	Retrospective, Observational	Aq	Not specified	5.6 +/− 0.31	NR	NR	11.52 +/− 0.79	NR	NR	*author specified score*; 60.9% eyes	Ex: 20.92 +/− 0.31
HUANG (2012)[25]	21/NR	Prospective, Observational	In	Active and Inactive TAO *b*	Active: 4.0 Inactive: 2.0	Active: 25.0 Inactive: 20.8	Active: 5.33 +/− 2.35 Inactive: 7.64 +/− 1.91	Active: 4.56 +/− 2.65 Inactive: 7.00 +/− 5.05	NR	NR	*author specified score*	Ex: 20.0
WU (2016)[56]	40/80	Prospective, Observational	Ev, Aq	Active and Inactive TAO *b, c* (Bartley criteria)	Active: 5.80 +/− 1.37 Inactive: 1.16 +/− 1.03	Active: 50.00 Inactive: 27.08	Active: 5.11 +/− 2.15 Inactive: 6.30 +/− 2.99	Active: 5.50 +/− 2.15 Inactive: 6.46 +/− 3.02	NR	NR	*author specified score*	Active Ex: 21.13 +/− 2.39 Inactive Ex: 19.78+/− 2.14
XU (2020)[26]	15/NR	Prospective, Interventional	In	Moderate-severe TED *a, c* (Bartley criteria)	Baseline: 4.0 +/− 1.07 Post-treatment: 2.47 +/− 0.74	Baseline: 40.04 +/− 26.42 Post – treatment: NR but improved	Baseline: 3.86 +/− 1.55 Post – treatment: NR but improved	Baseline: 7.60 +/− 2.90 Post – treatment:NR but improved	NR	NR	*author specified score*	Baseline Ex: 19.43 +/− 2.68 Post – treatment:: 18.1 +/− 1.84
ACHTSIDIS (2013)[12]	26/52	Prospective, Observational	Aq, Ev	Early Graves' Disease	NR; median 3.0 (1.75-4.0)	NR	Right eyes: 7.96 +/− 3.94 Left eyes: 8.26 +/− 4.21	Right eyes: 12.88 +/− 7.94 Left eyes: 14.04 +/− 9.00	NR	NR	NR	Ex: 17.65 +/− 2.30

*: Patients with a diagnosis of TED

a: Based on EUGOGO

b: Based on CAS

c: Author specifies diagnostic criteria

NR: not reported

Ex: Exophthalmos

Ev: Evaporative

Aq: Aqueous deficiency

In: Inflammatory

** This study reported combined data from both "study" and "non-study" eyes but did not specify how many eyes were in each category.