Egyptian Journal of Clinical Ophthalmology "*EJCO*"
An International peer-reviewed journal published bi-annually
Volume 5, Issue 1, July 2022: pp: 19-28 www. ejco.sohag-univ.edu.eg

*Original Article*

# ANTERIOR SEGMENT OPTICAL COHERENCE TOMOGRAPHY STUDY OF THE ANTERIOR OCULAR SURFACE IN THYROID EYE DISEASES

**Anwar, A.[1], Mahmoud, M.[1(*)], Hassan, H.[2] & Ahmed, A.[1]**
[1]Ophthalmology dept., Faculty of Medicine, Minia Univ., Egypt
[2]Internal Medicine dept., Faculty of Medicine, Minia Univ., Egypt

[*]*E-mail: drmsalah1982@yahoo.com*

Received: 9/3/2022
Accepted: 8/5/2022

## Abstract
***Purpose:*** *Use the anterior segment optical coherence tomography (AS-OCT) to evaluate the tear meniscus parameters, total corneal thickness (CT), and epithelial thickness in active and inactive thyroid eye disease (TED) patients and compare them with age-matched controls.* ***Patients and methods:*** *This is a prospective case-control clinical study in which the subjects were divided into three groups, group I of inactive thyroid patients, group II of active thyroid patients, and group III of healthy controls. The AS-OCT was used to measure lower tear meniscus parameters (tear meniscus height (TMH), tear meniscus depth (TMD), and tear meniscus area (TMA)), total CT, and epithelial thickness.* ***Results:*** *All tear meniscus parameters (TMH, TMD, and TMA) were reduced in groups I and II with more reduction in group II with no significant difference between them with a significant difference when comparing groups I and II with group III. The mean total CT was 496.7±19.9 in group I, 497.8±20.6 in group II, and 520.3±23.9 in group III with no significant difference (p-value = 0.757) between groups I and II while there was a significant difference when compared with healthy controls. The mean epithelial thickness was 46.5±2.6 in group I, 47.3±2.7 in group II, and 53.2±4.5 in group III with no significant difference between groups I and II while there was a significant difference when compared with healthy control.* ***Conclusion:*** *TED patients had reduced tear film parameters regardless of the thyroid activity, also the total CT and epithelial thickness was thinner in comparison with healthy controls.*

**Keywords:** *Anterior Segment Optical Coherence Tomography, Thyroid eye diseases-tear film.*

## 1. Introduction

Thyroid eye disease (TED), also known as Thyroid associated orbitopathy (TAO), is an autoimmune illness that causes inflammation, edema, and fibrosis in the orbital tissue. In adults, it is the most frequent orbital illness. TAO affects about 16 women and 3 males in every 100,000 people. Patients with TED suffer ocular discomfort symptoms such as irritation and a foreign body sensation, which are similar to those seen in patients with dry eye disease (DED) [1-3]. Patients with TED have a high prevalence of dry eye, with 65-85 % of them reporting symptoms [4]. The mechanism explaining the link between TED and DED is not entirely established, although the correlation is well-documented [5,6]. Schirmer's and fluorescein tear breakup time (TBUT) tests are two common clinical procedures

for evaluating the tear film that are used to investigate DED. They are, however, not always accurate, and none of them are sufficient for diagnosis on their own [7]. Optical Coherence Tomography (OCT) creates detailed cross-sectional images of the anterior and posterior segments using low coherence interferometry. OCT is a non-invasive, real-time method for evaluating the tear meniscus, total corneal thickness (CT), and corneal epithelial thickness [8,9]. Our study aimed to evaluate the thyroid activity on the precorneal tear film and the use of the AS-OCT to evaluate the tear meniscus parameters, CT, and epithelial thickness in active and inactive TED patients and compare them with age-matched controls.

## 2. Patients and Methods

This prospective case-control clinical study was performed in the Ophthal-mology Department, Minia University Hospital, Egypt between May 2021 and February 2022. Patients were divided into three groups. Group I included 70 eyes of 35 patients with thyroid inactive disease, group II included 70 eyes of 35 patients with thyroid active disease, and group III included 70 eyes of 35 healthy controls. The study was approved by the local ethics committee of the faculty of medicine of Minia University (Approval No: 165-2021) after obtaining written consent from each participant. Our study aimed to evaluate the thyroid activity on the tear film, CT, and epithelial thickness. The included thyroid patients had the systemic manifestation of graves' disease and abnormal thyroid functions with age between 20 to 60 years. The included patients either had no ocular manifestations or with TED as upper eyelid retraction, exophthalmos, typical restrictive strabismus, fluctuating lid edema, or chemosis/ caruncular edema. We excluded patients younger than 20 or older than 60 years, presence of systemic diseases such as diabetes mellitus (DM) and autoimmune diseases such as rheumatoid arthritis (RA) that may cause dry eye, previous ocular surgery, and use of contact lenses, smokers, pregnant women, and breastfeeding women. The patients were referred from the endocrinology clinic at Minia University Hospital. The activity of thyroid disease was decided by the endocrinologist depending on the clinical features of thyroid functions and laboratory levels of T3, T4, and TSH. Diagnosis of TED was based on two of the following three criteria: **1)** the presence of immune-related thyroid dysfunction (Grave's hyperthyroidism, Hashimoto thyroiditis, and circulating thyroid antibody) was diagnosed by an endocrinology specialist. **2)** Fusiform augmentation of at least one of the extraocular muscles was discovered on orbital computed tomography (CT) and/or (3) patients had at least 1 of the following typical orbital signs: upper eyelid retraction, exophthalmos, typical restrictive strabismus, fluctuating lid edema, or chemosis/caruncular edema [10]. Control subjects of normal persons attending to ophthalmology department for a routine check-up.

### 2.1. *Ophthalmologic examination*

All study subjects underwent a comprehensive ophthalmologic evaluation including history taking (previous medication intake, ocular surgery, trauma, and systemic diseases such as DM and rheumatic diseases), measurement of uncorrected and best-corrected using Log MAR charts, automated refraction, slit-lamp examination, intraocular pressure measurement, and fundus examination. Complete orbital examination with proptosis assessment by Hertel exophthalmometer (Handaya, Tokyo, Japan), eyelid examination with palpebral fissure height of more than 7 mm with exposure of the upper sclera, and EOM examination to decide the ocular manifestations of TED.

## 2.2. *AS-OCT technique*

Using the Avanti RTVue-XR platform (Optovue, Fremont, CA, USA) spectral domain OCT with the add-on lens of the corneal adaptor module (CAM-L mode: S/N 43386). All tests were performed at the same time of the day (between 10 AM to 12 PM ) to avoid confounding diurnal variation of measurements, in a dimly lit room and patients and controls were instructed not to use any eye drops, including artificial tear preparations, 2 h before testing. Multiple scans were captured until a good image of the tear meniscus at 6 'o'clock between the horizontal lid margin and the cornea.

2.2.1. Tear meniscus parameters

2.2.1.1. *Tear Meniscus Height (TMH)*

TMH, expressed in um, and represented by a line joining the points corresponding to the upper corneo-meniscus junction to the lower eyelid-meniscus junction

2-*Tear Meniscus Depth (TMD)*

TMD, expressed in um, and represented as the distance between the center of the upper boundary of the tear meniscus and the point at the bottom boundary where the cornea meets the eyelid.

3-*Tear Meniscus Area (TMA)*

TMA, as a triangular area formed by the corneal anterior boundary, anterior boundary of the lower eyelid, and anterior borderline of the tear meniscus and expressed in $mm^2$

2.3.1. Corneal pachymetry and epithelial thickness maps

A computer algorithm automatically maps the total CT (Pachymetry Map) and the corneal epithelial thickness (Epithelial Map) across the central 6 mm of the corneal surface. Each map is divided into 17 sectors (central, superior, inferior, superonasal, superotemporal, temporal, nasal, inferonasal and, inferotemporal). Only the central zone was used in our study, fig. (1)

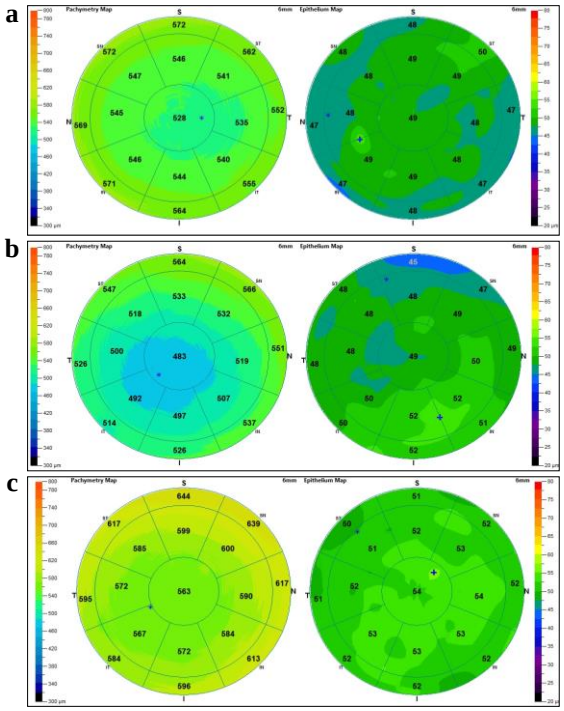


**Figure 1:** Pachymetry and epithelial maps; **a.** group I, **b.** group II, **c.** group III

### 2.3. *Tear Break-up time test (TBUT)*

The patient was requested to blink several times and then look straight ahead without blinking after a fluorescein strip (Fluorescein paper, Haag-Streit AG, Köniz, Switzerland) was put into the lower conjunctival sac. The tear film was examined using a slit-lamp biomicroscope with a cobalt blue filter. In seconds, the period between the last blink and the emergence of dark spots on the pre-corneal tear film was measured. The average of three scores was measured after repeating the test three times. Dry eye has a cut-off value of 10 seconds.

### 2.4. *Schirmer test*

Without anesthetic, a 5×35 mm strip of Schirmer filter paper (Schirmer tear test, Optitech Eyecare, Allahabad, India) was gently folded and put over the lower lid margin at the temporal angle at the intersection of the middle and lateral one-third of the eyelid. The patient was instructed to close her eyes during the treatment. The Schirmer I test value was determined by measuring the wet length of the strip after 5 minutes in millimeters (mm). In the Schirmer test (10 mm), there is a deficit in tear secretion.

### 2.5. *Methods of statistical analysis*

The statistical analysis was done by using IBM SPSS (Chicago, USA) statistical package version 20. For quantitative data: mean and standard deviation (SD) were used and for qualitative data: numbers and percentage were used. The comparison of quantitative data among three groups was done by the ANOVA and post hoc tests. While the comparison of quantitative data among three groups was done by the Chi-squared test. P-value was considered significant if < 0.05.

## 3. Results

### 3.1. *Demographic data*

Group I included 11 males and 24 females with a range of age 18 to 42 years, group II included 15 males and 20 females with a range of age 19 to 40 years, group III included 17 males and 18 females with a range of age 23 to 40 years, tab. (1)

**Table 1:** demographic data among studied groups:

| Variables | Group I | Group II | Group III | p-value | | |
|---|---|---|---|---|---|---|
| | | | | *All* | | |
| | *N=35 patients* | *N=35 patients* | *N=35 patients* | Group I vs group II | Group I vs group III | Group II vs group III |
| **Age:** | 28.4±8.1 | 27.6±5.1 | 30.4±5.4 | 0.872 | | |
| **mean ±SD:** | | | | | | |
| **Range:** | 18-42 | 19-40 | 23-40 | 0.441 | 0.679 | 0.784 |
| **Sex: n (%)** | | | | 0.744 | | |
| **Females** | 24(68.6%) | 20(57.1%) | 18(51.4%) | 0.765 | 0.621 | 0.833 |
| **Males** | 11(31.4%) | 15(42.9%) | 17(48.6%) | | | |

### 3.2. *Tear meniscus parameters*

All tear meniscus parameters, figs. (2, 3, 4) were reduced in groups I and II with more reduction in group II with no significant difference between them in TMH, TMA, and TMD (0.616, 0.406, and 0.431 respectively) with a significant difference when comparing groups I and II with group III (p-value <0.001) , tab. (2)

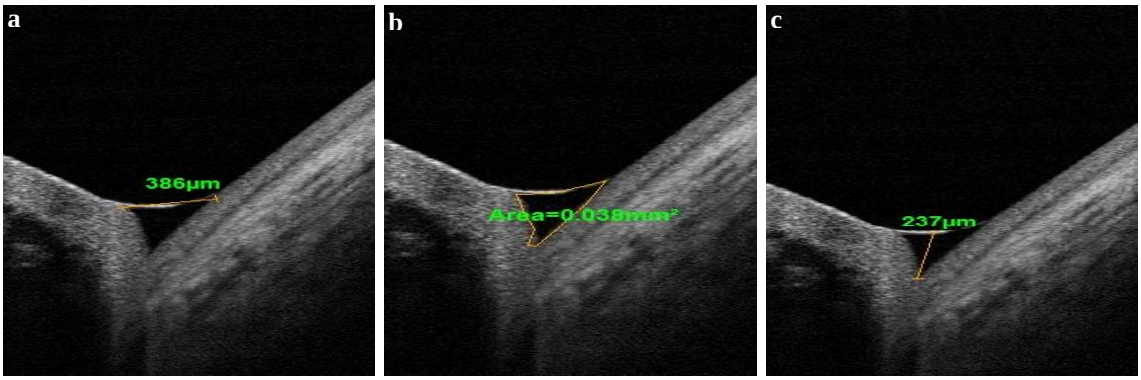


**Figure 2:** AS-OCT images of one eye of group I patients; **a.** TMH, **b.** TMA, **c.** TMD.

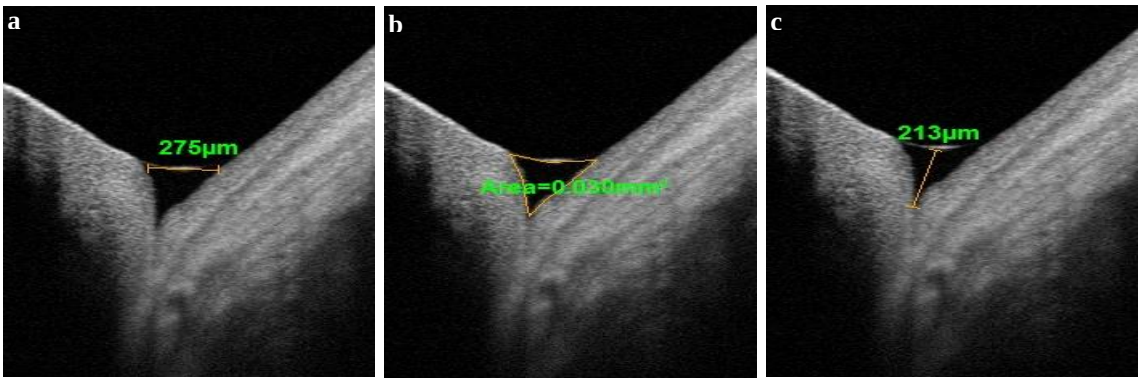


**Figure 3:** AS-OCT images of one eye of group II patients; **a.** TMH, **b.** TMA, **c.** TMD.

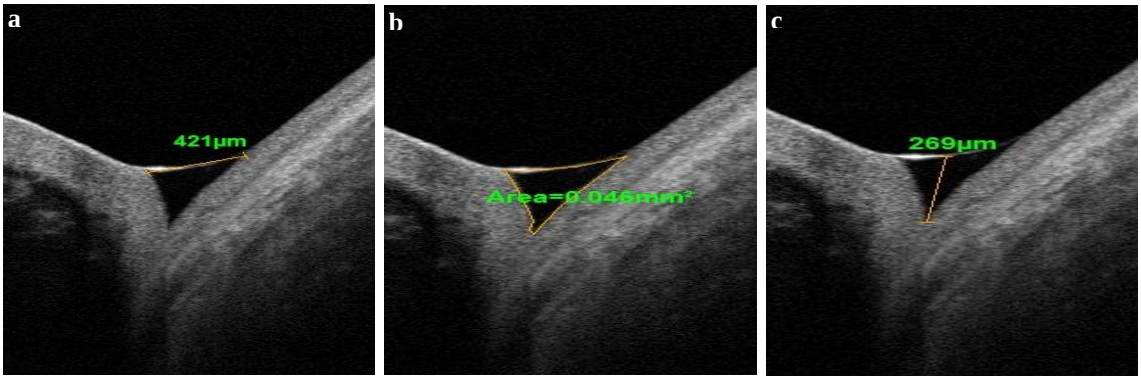


**Figure 4:** AS-OCT images of one eye of group III patients; **a.** TMH, **b.** TMA, **c.** TMD.

**Table 2:** Tear meniscus parameters, TBUT and Shirmer's test

| Variables | Group I | Group II | Group III | p-value | | |
|---|---|---|---|---|---|---|
| | *N=70* | *N=70* | *N=70* | *All* | | |
| | Mean ±SD | Mean ±SD | Mean ±SD | Group I vs group II | Group I vs group III | Group II vs group III |
| **TMH** | 339.3±99.5 | 329.1±100.4 | 480.0±154.4 | <0.001 | | |
| | | | | 0.616 | <0.001 | <0.001 |
| **TMA** | 0.04±0.06 | 0.039±0.02 | 0.06±0.04 | 0.001 | | |
| | | | | 0.406 | 0.005 | <0.001 |
| **TMD** | 244.5±79.3 | 233.0±80.9 | 334.2±98.0 | <0.001 | | |
| | | | | 0.431 | <0.001 | <0.001 |
| **BUT** | 7.6±1.9 | 7.1±1.7 | 12.6±0.9 | <0.001 | | |
| | | | | 0.053 | <0.001 | <0.001 |
| **Shirmer** | 6.4±1.4 | 6.4±1.07 | 13.7±1.09 | <0.001 | | |
| | | | | 0.983 | <0.001 | <0.001 |

### 3.3. *BUT and Shirmer's test*

BUT and Shirmer's tests were reduced in groups I and II with more reduction in group II with no significant difference between them (p-value= 0.053 and 0.983 respectively) while there was a significant difference when comparing groups I and II with group III, tab. (2) & figs.(1, 2, 3)

### 3.4. *Total CT and epithelial thickness*

The mean total CT was 496.7±19.9 in group I, 497.8±20.6 in group II, and 520.3±23.9 in group III with no significant difference (p-value= 0.757) between group I and 2 while there was a significant difference when compared with healthy controls. The mean epithelial thickness was 46.5±2.6 in group I, 47.3±2.7 in group II, and 53.2±4.5 in group III with no significant difference (p-value= 0.183) between group I and II while there was a significant difference when compared with healthy control, tab. (3).

**Table 3:** The total CT and epithelial thickness

| Variables | Group I | Group II | Group III | p-value | | |
|---|---|---|---|---|---|---|
| | | | | *All* | | |
| | *N=70* | *N=70* | *N=70* | Group I vs group I I | Group I vs group III | Group II vs group III |
| **CT** | 497.8±20.6 | 496.7±19.9 | 520.3±23.9 | <0.001 | | |
| | | | | 0.757 | <0.001 | <0.001 |
| **Epithelial Thickness** | 47.3±2.7 | 46.5±2.6 | 53.2±4.5 | <0.001 | | |
| | | | | 0.183 | <0.001 | <0.001 |

## 4. Discussion

Thyroid problems are prevalent in diverse parts of Egypt, with a high proportion of these disorders being observed in Upper Egypt [11]. Patients with TED have a significant prevalence of dry eye, with 65-85 percent of them reporting symptoms such as visual impairment, ocular pain, and tear film instability. Reduced aqueous tear production due to lacrimal gland involvement; excessive tear evaporation due to increased ocular surface exposure; high osmolarity of tears, meibomian gland dysfunction due to incomplete blinking; and abnormal friction between the ocular surface and the eyelid due to increased eyelid pressure and ocular surface inflammation are all suspected mechanisms for DED development in TED [12,13]. More than half of all asymptomatic patients demonstrate clinical signs of dry eye. SO, it is important to examine these patients regularly to avoid discomfort and corneal damage. Unfortunately, the diagnosis of DED could not be assessed by a single test as some tests are used to evaluate tear film quality, other tests are used for tear film quantity, tear film osmolarity and tear evaporation rate [14]. Schirmer's test and TBUT were the traditional diagnostic methods for tear film evaluation by most ophthalmologists in ophthalmic practice because of they are easy to use, inexpensive, and take a short time to perform but these tests were invasive with low reproducibility and repeatability; reflex tearing and lack of the control over reflex lacrimation with other factors that may interfere with the results. So there was a need for a non-invasive, quick, reliable, and comfortable test with significant advancement in diagnostic approaches of the tear meniscus such as video assessment, noninvasive interference tear meniscometry, and optical pachymetry but these methods were complicated with low accuracy rates and are not widely used in ophthalmic practice. The AS-OCT is a reliable non-invasive real-time tool for quantitative evaluation of tear film meniscus, suggesting the pos-

sibility of AS-OCT as a tool for diagnosis and follow-up of DED [15-18]. Our study aimed to use the AS-OCT to evaluate the tear film in TED and study the effect of thyroid activity on the tear film, total CT, and epithelial thickness and compare the active and inactive thyroid patients with healthy controls of similar age groups. We imaged the tear film under some precautions to avoid false values as no previous eye drops or topical artificial tears. Imaging was done at a similar time in all patients to avoid misleading diurnal variations by the same observer. Also, AS-OCT images were captured at least 3 times to obtain an image of good quality. Thyroid patients were split into two groups: active and inactive, based on a systematic examination of thyrotoxicosis signs, ocular manifestations of thyrotoxicosis and laboratory T3, T4, and TSH levels evaluated by an endocrinology specialist. Our results showed a reduction of the tear meniscus parameters in the active and inactive stages with no significant difference between them (p-value= 0.616, 0.406, and 0.431) in TMH, TMA, and TMD respectively with significant difference (p-value <0.001) when compared with healthy controls. This indicated TED had significant dry eye regardless of the thyroid activity. BUT and Shirmer's tests were reduced in thyroid patients in comparison with healthy controls with more reduction in the active state. This indicates that TED had an evident effect on the tear film regardless of the thyroid activity. Our results agreed with the study done by Allam et al., who compared ocular surface parameter changes in active and inactive TED patients and controls and revealed that active TED patients had more decreased tear secretion than inactive TED patients (p= 0.012). But our study did not evaluate the meibomian glands [19]. In addition, Gürdal et al., discovered that TED had considerably lower Schirmer test levels than normal controls [20]. Furthermore, a research by Park et al., active TED patients exhibited lower basal tear secretion than inactive TED patients (p=0.024) [13]. The existence of exophthalmos, upper eyelid retraction, and lagophthalmos can explain the lower Schirmer test findings. Furthermore, tear secretion is reduced in TED patients due to damage to the lacrimal gland caused by autoantibodies attacking the thyroid-stimulating hormone receptor present in the lacrimal glands. Membrane-associated mucin present on the microvilli of the cornea and conjunctiva, as well as secretory mucin of the goblet cells of the conjunctiva, impair the tear film's stability. Nowak et al., discovered that tear break-up time was considerably lower in TED patients with dry eye (5.843.31 s) than in controls (11.43.75), implying an unstable tear film [21]. Gupta et al., found that less than one-third of their patients had a reduced TBUT [22]. A study by Sizmaz et al., evaluated the tear meniscus in patients with Graves' disease (GD) which were divided into three groups, group I without clinical features of thyroid-associated ophthalmopathy (TAO), group II of patients with signs of TAO, and group III of healthy participants and resulted in TMH and TMA did not significantly differ between groups I and II with a significant difference with group III [23]. Also, a study by Ha et al., evaluated the dry eye in TAO according to disease activity and revealed that TFBUT was shorter in the active TAO group than in the inactive TAO group [24]. Regarding the total CT and epithelial thickness, our study revealed that total CT and epithelial thickness were thinner in thyroid patients in comparison with healthy controls. This agreed with Carreira et al., who assessed the tear film stability and corneal epithelial thickness in patients with GD with and without Graves orbitopathy and showed that the level of eye dryness and corneal thinning were higher in GD regardless of GO status [25]. A study by Bassioujny et

al., who used the Pentacam (Oculus Optikgeräte GmbH) to evaluate the cornea of patients with thyroid gland dysfunction and controls and revealed that patients with hyperthyroidism tend to have thinner corneas and more abnormal tomographic parameters correlating with keratoconus [26]. Alternative research on tear film evaluation used other methods in TED, such as Alanazi et al., who employed the phenol red thread test followed by the TBUT test with a 10-min break between the tests. The phenol red thread test resulted in acceptable tear volumes of 11.78.1 and 10.57.3 mm, respectively, however, these were significantly lower (P= 0.05) than the control group's (22.26.5 and 20.75.2 mm, respectively). Furthermore, the TBUT with thyroid issues showed a degree of eye dryness, whereas the control group had normal eye scores [27]. The tear evaporation rate was evaluated by Abusharaha et al., who used a vapometer and found that the average tear-evaporation rate in the study group (median 41.2 [IQR 41.4] g/m2h) was substantially greater than the control group (15.7 [13.7] g/m2h) [28]. Takahashi et al., conducted another investigation on tear film break-up patterns in TED patients and found that line breaks were more frequently observed in TED, while random breaks in the simple dry eye are usually only associated with minor ocular surface damages, those in TED were associated with a higher incidence of concomitant superior limbic keratoconjunctivitis [29]. Kemal et al., examined tear osmolarity and found that TED patients had significantly greater tear osmolarity levels than healthy controls (p= 0.001). The active subgroup had significantly higher tear osmolarity than the inactive category (p= 0.003). As a result, they proposed that tear osmolarity measurement should be added to existing tests for identifying dry eye severity and disease activity in Graves ophthalmopathy (GO) patients [30]. Several obstacles hampered our research. A modest number of patients were included in this investigation. Also, the tear film lipid layer and tear film osmolarity were not assessed, which could have provided more information on dry eye. In addition, the duration of thyroid illness was not assessed. We were unable to obtain specific information about Thyroid autoantibody (TRAb) levels, which could have a link to ocular affection, as a previous study found a link between TRAb and TED [31]. Also, we did not differentiate between the different manifestations of TED as lid retraction, proptosis, and EOM enlargement and their effect on the tear film and the cornea.

## 5. Conclusion

*In conclusion, patients with thyroid disorders had significantly higher levels of eye dryness than normal subjects, with increased severity during the active phase of the disease and the persistence of dry eye manifestations during the inactive phase due to a variety of factors such as lid retraction, proptosis, lacrimal gland affection, and other factors. As a result, topical lubricants had a role in lowering ocular irritation and smoothing the ocular surface, resulting in improved vision and relief from debilitating symptoms. In addition, the total CT and epithelial thickness were lower than in the normal control group, which should be taken into account when evaluating IOP and other ocular examinations to avoid misinterpretations. AS-OCT was a reliable noninvasive method for tear film assessment, total CT, and epithelial thickness in patients with thyroid disorders.*

## References


1. Smith, T. & Hegedüs, L. Graves' disease. ***N Engl J Med***. 2016; 375 (16): 1552-1565.
2. Bruscolini, A, Abbouda, A., Locuratolo, N., et al. Dry eye syndrome in non-exophthalmic graves' disease. ***Semin Ophthalmol***. 2015; 30 (5-6): 372-376.
3. Rizvi, S., Rana, V., Sheelu, S., et al. Dry eye evaluation in thyroid associated orbitopathy. ***Int J Ocul Oncol Ocul***. 2016; 2 (2): 90-94
4. Rizvi, S., Rana, V., Sheelu, Siddiqi, S., et al. Dry eye evaluation in thyroid

associated orbitopathy. ***IP Int J Ocul Oncol Oculoplasty*** 2016; 2 (2): 90-94

**5.** Turkyilmaz, K., Öner, V., Şahin, S., et al. Tear film osmolarity in patients with Graves ophthalmopathy. ***Eur J Gen Med***. 2014; 11 (1): 15-19.

**6.** Selter, J., Gire, A. & Sikder, S. The relationship between Graves' ophthalmopathy and dry eye syndrome. ***Clin Ophthalmol***. 2015; 9: 57-62.

**7.** Srinivasan, S. & Nichols, K. Collecting tear osmolarity measurements in the diagnosis of dry eye. ***Expert Rev Ophthalmol***. 2009; 4: 451-3.

**8.** Raj, A., Dhasmana, R. & Nagpal, R. Anterior segment optical coherence tomography for tear meniscus evaluation and its correlation with other tear variables in healthy individuals. ***J Clin Diagn Res***. 2016; 10 (5): NC01-4.

**9.** Li, Y., Tan, O., Brass, R., et al. Corneal epithelial thickness mapping by Fourier-domain optical coherence tomography in normal and keratoconic eyes. ***Ophthalmology***. 2012; 119 (12): 2425-2433.

**10.** Bahn, R. Graves' ophthalmopathy. ***N Engl J Med***. 2010; 362 (8): 726-738

**11.** Elzahry, M. Patterns of thyroid disorders in Qena population: A hospital-based descriptive study. ***Int. Medicine***. 2019; 1. 204. 10.5455/im.49650.

**12.** Selter, J., Gire, A. & Sikder, S. The relationship between Graves' ophthalmopathy and dry eye syndrome. ***Clin. Ophthalmol***. 2015, 9: 57-62.

**13.** Park, J. & Baek, S., et al. Dry eye syndrome in thyroid eye disease patients: The role of increased incomplete blinking and meibomian gland loss. ***Acta Ophthalmol***. 2019; 97 (5): e800-e806.

**14.** Abusharaha, A., Alturki, A., Alanazi, S., et al. An assessment of the tear evaporation rate in thyroid gland patients. ***Clin Ophthalmol***. 2019; 13: 131-135.

**15.** Nichols, K., Mitchell, G. & Zadnik, K. The repeatability of clinical measurements of dry eye. ***Cornea***. 2004; 23: 272-285.

**16.** Yokoi, N. & Kumuro, A. Non-invasive methods of assessing the tear film. ***Exp Eye*** Res. 2004; 78: 399-407.

**17.** Nichols, K., Nichols, J. & Mitchell G. The lack of association between sing and symptoms in patients with dry eye disease. ***Cornea***. 2004; 23: 762-770

**18.** Stegmann, H., Aranha Dos Santos, V., Messner, A., et al. Automatic assessment of tear film and tear meniscus parameters in healthy subjects using ultrahigh-resolution optical coherence tomography. ***Biomed Opt Express***. 2019; 10 (6): 2744-2756

**19.** Allam, I., Lazreg, S., Shafik Shaheen, M., et al. Ocular surface changes in patients with thyroid eye disease: An observational clinical study. ***Clin Ophthalmol***. 2021; 15: 2481-2488

**20.** Gürdal, C., Saraç, Ö., Genç, İ., et al. Ocular surface and dry eye in Graves' disease. ***Curr Eye Res***. 2011; 36 (1): 8-13.

**21.** Nowak, M., Marek, B., Kos-Kudła, B., et al. Ocena stanu filmu lzowego u chorych z aktywna postacia orbitopatii tarczycowej [Tear film profile in patients with active thyroid orbithopathy]. ***Klin Oczna***. 2005; 107 (7-9): 479-482.

**22.** Gupta, A., Sadeghi, P. & Akpek, E. Occult thyroid eye disease in patients presenting with dry eye symptoms. ***Am J Ophthalmol***. 2009; 147 (5): 919-923.

**23.** Sizmaz, S., Altan-Yaycioglu, R., Bakiner, O., et al. Assessment of tear meniscus with optical coherence tomography in thyroid-associated ophtalmopathy. Current Eye Research. 2014; 39 (4): 323-328.

**24.** Ha, J., Choi, W. & Yoon, K. Clinical Features of dry eye in thyroid-associated ophthalmopathy according to disease activity. ***J. of the Korean Ophthalmological Society***. 2016; 57: 1037-1043.

**25.** Carreira, A., Rodrigues-Barros, S., Moraes, F., et al. Impact of Graves'

disease on ocular surface and corneal epithelial thickness in patients with and without graves orbitopathy. ***Cornea***. 2021; 41(4): 443-449.

**26.** Bassiouny, R., Awad, E., Gaafar, W., et al. Corneal tomographic analysis among patients with thyroid gland dysfunction. ***J Refract Surg***. 2021; 37 (3): 192-197.

**27.** Alanazi, S., Alomran, A., Abusharha, A., et al. An assessment of the ocular tear film in patients with thyroid disorders. ***Clin Ophthalmol***. 2019; 13: 1019-1026

**28.** Abusharaha, A., Alturki, A., Alanazi, S., et al. Assessment of tear-evaporation rate in thyroid-gland patients. ***Clin Ophthalmol***. 2019; 13: 131-135.

**29.** Takahashi, Y., Lee, P., Vaidya, A. et al. Tear film break-up patterns in thyroid eye disease. ***Sci Rep***. 2021; 11: 5288.

**30.** Turkyilmaz, K., Öner, V., Sahin, S., et al. Tear film osmolarity in patients with Graves ophthalmopathy. ***Eur J Gen***, 2014; 11 (1): 11-19.

**31.** Nicolì, F., Lanzolla, G., Mantuano, M., et al. Correlation between serum anti-TSH receptor autoantibodies (TRAbs) and the clinical feature of Graves' orbitopathy. ***J Endocrinol Invest***. 2021; 44 (3): 581-585.