



# An examination of the ocular surface parameters of patients with non-exophthalmic Graves disease

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## Abstract

**Aim:** To evaluate patients with non-exophthalmic Graves Disease (GD) in respect of ocular surface and tear film abnormalities, central corneal thickness (CCT) and central corneal epithelial thickness (CCET) values.

**Materials and Methods:** This prospective research included non-exophthalmic patients referred to the ophthalmology outpatient clinic because of GD in 2022-2023. In all patients, dry eye was evaluated with tear break-up time (TBUT) and the Schirmer test, and the CCT and CCET values were measured using Spectral-Domain anterior segment optical coherence tomography (AS-OCT).

**Results:** The data of a group of 26 patients with GD, comprising 14 males and 12 females with a mean age of  $43.27 \pm 15.25$  years were compared with a control group of 26 healthy individuals, comprising 13 males and 13 females with a mean age of  $41.69 \pm 13.4$  years. No statistically significant difference was determined between the two groups in respect of age and gender ( $p=0.694$ ,  $p=0.781$  respectively). The TBUT values of both eyes were statistically significantly lower in the GD patients compared to the control group ( $p<0.001$ ). All other values were similar in both groups ( $p>0.05$ ).

**Conclusion:** The findings suggest that tear film abnormalities occur in GD patients before Graves orbitopathy (GO) develops or even in inactive GO. Therefore, it is important that the ocular surface is evaluated regularly in GD patients, irrespective of GO status.



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## Introduction

Graves disease (GD) is an organ specific, autoimmune disease that occurs when antibodies against the thyroid stimulating hormone (TSH) receptor overstimulate the thyroid gland. It constitutes 80% of hyperthyroidism cases and is seen approximately 6-fold more in females than in males (3% vs. 0.5%) [1-5]. Goiter, weight loss, heat intolerance, and tachyarrhythmia are considered the typical clinical features [5]. GD is a disease characterized by hyperthyroidism and diffuse goiter, as well as ophthalmopathy and dermatopathy [6].

The most common extrathyroidal finding of GD is Graves orbitopathy (GO), which develops in >50% of patients [7]. Functional disorders of autoantibodies, cytokines and lymphocytes play a role in the etiology. Inflammation caused by lymphocyte infiltration in GO leads to edema of extraocular muscles and orbital fat tissue, proptosis, eyelid

retraction, pain in the orbit, and an increase in orbital volume. There may also be the development of complications such as congestion, chemosis, photophobia, exposure keratopathy, corneal ulceration, eyelid edema, diplopia, and optic nerve decompression that may result in vision loss [8-10]. Nevertheless, ocular symptoms are not reported by most patients with GO [11].

There are many reports in literature of tear film layer abnormalities in patients with Graves' ophthalmopathy have been frequently shown in the literature [11-13]. Dry eye prevalence in GO patients has been reported to be 60% [12]. With increased ocular exposure, eyelid retraction and proptosis occur. An increase in the aqueous component of the tear film and/or evaporation is known to cause dry eye disease (DED) [11-14]. It is thought that inflammation in corneal epithelial cells resulting from tear film instability and hyperosmolarity caused by DED on the ocular surface may affect corneal morphology, causing a change in central corneal epithelial thickness (CCET) [15].

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The central corneal thickness (CCT) and CCET are measured using anterior segment optical coherence tomography (AS-OCT).

There are few studies in the literature on the ocular surfaces of patients with inactive GO or GD who do not have clinically significant ocular involvement. The aim of this study was to evaluate the ocular surface and tear film abnormalities, CCT and CCET values in GD patients without significant ocular involvement.

## Materials and Methods

Approval for the prospective study was obtained by the Ethics Committee of Firat University Faculty of Medicine, and it was also carried out in accordance with the principles of the Declaration of Helsinki (approval no: 2023/02-24). Fifty-two eyes of 26 patients who were evaluated for GD in our clinic between 2022 and 2023 were included in the study. The included patients did not have thyroid orbitopathy and had low clinical activity scores (CAS) according to the European Group GO Consensus Statement criteria were included in the study. As the control group, 52 eyes of 26 healthy volunteers without ocular or systemic disease were included in the study. Study exclusion criteria included history of ocular surgery/trauma, active smoking, eyelid/eyelash abnormalities, corneal pathology, contact lens wear, presence of other eye disease (eg, retinopathy, glaucoma, and uveitis), high refractive error (6 diopters spherical, 3 diopter cylindrical), pregnant/breastfeeding women, or any additional diagnosis of systemic disease.

The GO diagnosis was based on the criteria of the European Group GO Consensus Statement. The activity of the disease was evaluated using the clinical activity score (CAS). In the scoring system, which is based on 4 classical signs of inflammation (pain, redness, swelling and dysfunction), only 7 items [16] are considered at the beginning and the total score is calculated as the sum of the scores given to each of the items evaluated. A CAS score of 3/7 in the first examination or  $\geq 4/10$  in subsequent evaluations is accepted as clinically active disease [2]. All patients included in the study scored below these criteria.

All individuals in the control and patient groups were evaluated by a single ophthalmologist. Best corrected visual acuity was evaluated using the Snellen chart. Anterior segment examination was performed with slit lamp examination. Goldman applanation tonometry was performed last because of the risk of being invasive and affecting corneal thickness. AS-OCT was used for CCT and CCET measurement (Spectral-Domain AS-OCT; OCT HS100, Canon, Australia). The mean corneal and central corneal epithelial thickness was 5 mm. Since the quality of the image obtained in the measurements made from the perilimbal cornea region (7-9 mm) was not at an acceptable level, it was not included in the analysis.

Dry eye was evaluated using tear break-up time (TBUT) and Schirmer test. In the TBUT test, the time elapsed until the first dry spot after blinking was observed with cobalt blue after 2% sodium fluorescein was dropped into the eye. The average of three consecutive measurements was taken. In the Schirmer test, after local anesthetic

drops (oxybuprocaine chloride) were dropped into the eye, a Schirmer strip (5x35 mm) was placed in the inferior temporal fornix. The patient was allowed to close his eyes. After five minutes, aqueous tear secretion was determined by measuring the wet part of the paper.

## Statistical analysis

Data obtained in the study were analyzed statistically using SPSS version 22.0 software (Statistical Package for the Social Sciences version 21.0, SPSS Inc., Chicago, IL, USA). Intergroup variables were presented as numbers (n) and percentage (%). Chi-square test was used for comparisons between groups. Whether the continuous numerical variables fit the normal distribution was evaluated using the Shapiro-Wilk test. Independent Samples t-test and Mann Whitney U tests were used for the analysis of parameters that were normally distributed and not normally distributed. Categorical variables are stated as number and percentage. Numerical variables conforming to normal distribution are presented as mean  $\pm$  standard deviation values and those not showing normal distribution as median (1st quartile - 3rd quartile) values. A P value of  $<0.05$  was considered statistically significant.

## Results

Evaluation was made of a group of 26 patients (F/M:12/14) with GD a mean age of  $43.27 \pm 15.25$  years, and a control group of 26 healthy individuals (F/M:13/13) a mean age of  $41.69 \pm 13.4$  years. No statistically significant

**Table 1.** Comparison of results in the Graves disease patients and the control group.

	Group		p
	Control (n = 26)	Graves (n = 26)	
Age, years (mean $\pm$ SD)	41.69 $\pm$ 13.4	43.27 $\pm$ 15.25	0.694*
Gender, n (%)			
Male	13 (50.0%)	14 (53.8%)	0.781**
Female	13 (50.0%)	12 (46.2%)	
TBUT right (sec)	15 (10 - 15)	6 (5 - 6)	<b>&lt;0.001</b>
TBUT left (sec)	12.73 $\pm$ 3.09	6 $\pm$ 1.9	<b>&lt;0.001*</b>
Schirmer right (mm)	15 (10 - 18)	11.5 (10 - 13)	0.102
Schirmer left (mm)	13 (10 - 16)	12 (11 - 14)	0.472
CCT right	537.5 (519 - 556)	552.5 (532 - 562)	0.053
Central CCET	53.58 $\pm$ 2.4	52.96 $\pm$ 2.86	0.405*
Superior CCET	50.5 (48 - 52)	50 (48 - 52)	0.612
Inferior CCET	53.88 $\pm$ 2.82	53.31 $\pm$ 3.08	0.485*
Nasal CCET	52 (50 - 54)	50.5 (49 - 54)	0.367
Temporal CCET	51.69 $\pm$ 2.87	50.85 $\pm$ 3.79	0.368*
CCT left	537.73 $\pm$ 21.79	546.35 $\pm$ 18.72	0.132*
Central CCET	53.81 $\pm$ 2.45	53.92 $\pm$ 2.45	0.866*
Superior CCET	50.5 (48 - 52)	50 (49 - 53)	0.658
Inferior CCET	53.31 $\pm$ 3.41	53.73 $\pm$ 2.66	0.620*
Nasal CCET	51.65 $\pm$ 2.87	52.38 $\pm$ 3.1	0.382*
Temporal CCET	51.5 (50 - 54)	50 (49 - 53)	0.555

CCT: Central Corneal Thickness, CCET: Central Corneal Epithelial Thickness, TBUT: Tear Break Up Time \*Independent samples t-test

\*\*Chi-square test. Mann Whitney U test was used for other comparisons.

difference was determined between the GD group and control group in respect of age and gender ( $p=0.694$ ,  $p=0.781$  respectively). The TBUT values of both eyes were statistically significantly lower in the GD group than in the control group ( $p<0.001$ ). All the other values showed no statistically significant difference between the GD group and control group ( $p>0.05$ ). The clinical characteristics and demographic characteristics of all patients participating in the study are given in Table 1.

## Discussion

The International Dry Eye Workshop (DEWS) II states that for the diagnosis of DED, in addition to the decrease in tear break-up time, tear film hyperosmolarity and staining on the ocular surface, the presence of ocular symptoms should be determined with valid questionnaires [17]. Dry eye symptoms are frequently seen secondary to inflammation in ophthalmopathy associated with Graves' disease. In these patients, eyelid retraction and proptosis occur, resulting in increased globe exposure. Consequently, it is thought that dry eye occurs with mechanisms such as aqueous deficiency of tears and evaporation in the tear film [18]. Recent studies have shown that patients with GD who do not have exophthalmos may have damage to the cornea with deterioration in the tear film, and it is thought that there may be other causes of dry eye in patients with GD, and that abnormalities on the ocular surface may occur before the onset of GO [18-20]. It has been shown in various studies that tear film and corneal damage develop in patients with GD without significant GO [2, 11, 21, 22]. Previous reports examining the epithelial thickness profile in DED have shown inconsistent results [15, 23-25]. The aim of the current study was to compare deficiencies in the tear film layer and the CCT and CCET values between patients with inactive GO according to CAS, and a healthy age and gender-matched control group. The study results demonstrated significantly lower TBUT values in both eyes in the GD group without significant thyroid orbitopathy findings compared to the control group. These results are consistent with the reports in literature that have lower TBUT values in GD patients [12, 22, 26]. Grdal et al. reported no difference between GD patients with and without GO in respect of OSDI, TBUT and Schirmer values, which are clinical diagnostic scores of DED, [22]. Carreira et al. found higher rates of significant ocular surface disorder in patients with GD presenting with a clinical diagnosis of DED, in patients with and without GO compared with a healthy control group (GO vs. no GO, GO vs controls: 77.77%-75%), higher OSDI scores (GO - GD without GO - controls: 15.44 - 15.06 - 9.88) and lower TBUT values (GO - GD without GO - controls: 6.33 sec - 7.25 sec - 11.63 sec) [26]. These results indicate that GD may initiate an inflammatory cascade resulting in epithelial and stem cell damage and be associated with a reduced TBUT value, early tear film imbalance, and abnormal tear film homeostasis. No consensus has yet been reached regarding the effect of DED on corneal thickness, and discussions still continue [27]. Craig, Erdelyi, and Villani reported that DED is associated with thinning of the corneal epithelium, especially in the upper quadrant, while Fabiani, Chen, and Kanelopoulos stated that dry eye is

an indicator of increased epithelial thickness [23, 28-32]. In a study by Carreira et al., no statistically significant difference was found in CET measurements between patients with or without GO ( $p>0.05$ ). These results were attributed to prolonged ocular surface inflammation, eyelid retraction, and proptosis in the non-GO subset of patients with GD. There was no correlation between tear film evaluation parameters (OSDI, TBUT, and Schirmer's test) and CET measurements, and CAS correlated with mean superior CET ( $p = 0.03$ ,  $r = -0.31$ ). According to the results of the study, although corneal damage may occur in GD patients with or without GO, corneal epithelial thinning is thought to be more pronounced in patients with GO [26]. Finally, when we looked at the results of our study, we saw that there was no significant difference between the groups in terms of the central 5 mm mean CCT and CCET values. We think that more comprehensive studies with a large number of patients should be conducted to evaluate the effect of Graves' disease on CCT and CCET.

## Limitations

The limitations of this study include the small number of patients and the absence of a group with active GO.

## Conclusion

The results of this study show us that those with Graves' disease may have tear film abnormalities even in the absence of graves ophthalmopathy. This indicates that the ocular surface should be evaluated at regular intervals in patients with GD, regardless of the presence of GO. A greater awareness of dry eye symptoms may allow a faster and more careful diagnostic and therapeutic approach in GD patients without GO.

## Ethical approval

It was approved by the Firat University Clinical Research Ethics Committee with the decision dated 31.01.2023 and numbered 14136.

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