

# Tear Film Osmolarity in Patients with Graves Ophthalmopathy



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## ABSTRACT

To investigate changes of tear osmolarity in patients with Graves ophthalmopathy (GO). Twenty-three patients with GO (GO group) and 25 healthy controls (control group) were enrolled in the study. GO patients were divided into two subgroups as active GO and inactive GO subgroups. Orbital inflammatory activity was evaluated using the clinical activity score (CAS). Tear osmolarity was measured using TearLab Osmolarity System (TearLab™ Corp., San Diego, CA). The GO patients had significantly higher tear osmolarity levels than the healthy controls ( $p<0.001$ ). Tear osmolarity levels were significantly higher in active GO subgroup than in inactive GO subgroup ( $p=0.003$ ). We have revealed that GO patients had significantly higher tear osmolarity levels than healthy controls. In addition, there was a relationship between the disease activity and tear osmolarity. Therefore, we suggest that tear osmolarity measurement may be added to other tests for diagnosing dry eye severity in GO and it may be useful to evaluate the disease activity in patients with GO.

**Key words:** Graves ophthalmopathy, tear osmolarity, dry eye disease

## Graves Oftalmopati Hastalarda Gözyaşı Film Ozmolaritesi

### ÖZET

Graves oftalmopati (GO)'li hastalarda gözyaşı osmolarite değişikliklerini araştırmak. Yirmiiç GO hastası (GO grubu) ve 25 sağlıklı gönüllü (kontrol grubu) çalışmaya dahil edildi. GO grubu da aktif ve inaktif GO grupları olmak üzere iki alt gruba ayrıldı. Orbital inflamasyon aktivitesi klinik aktive skoru (KAS) esas alınarak hesaplandı. Gözyaşı osmolaritesi TearLab Osmolarite Sistemi (TearLab™ Corp., San Diego, CA) kullanılarak ölçüldü. GO grubu kontrol grubuna göre anlamlı derecede daha yüksek gözyaşı osmolarite değerlerine sahipti ( $p<0.001$ ). Ayrıca aktif GO alt grubu inaktif GO alt grubuna göre anlamlı derecede yüksek gözyaşı osmolarite değerlerine sahipti ( $p=0.003$ ). Bu çalışmada GO hastalarında gözyaşı osmolaritesinin kontrol grubuna göre anlamlı derecede daha yüksek olduğunu gösterilmiştir. Ayrıca hastalık aktivitesi ile gözyaşı osmolaritesi arasında bir ilişki tespit edilmiştir. Bu nedenle GO hastalarında gözyaşı osmolaritesi kuru göz ciddiyetinin teşhisinde ve GO hastalığının aktivitesinin belirlenmesinde diğer testlerle beraber yardımcı olabileceğini düşünmekteyiz.

**Anahtar kelimeler:** Graves oftalmopati, gözyaşı osmolaritesi, kuru göz

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## INTRODUCTION

Graves ophthalmopathy (GO) is an autoimmune disorder characterized by inflammation, edema, and fibrosis at the orbital tissue. It is the most common orbital disease in adults (1). IgG antibody may be responsible for hypertrophy of the extraocular muscles, cellular infiltration of the interstitial tissues, and proliferation of orbital fat and connective tissue (2). Patients with GO have symptoms of ocular discomfort including redness, irritation, and foreign body sensation, which are similar to those observed in dry eye disease (DED) (3-5). Some methods such as tear break-up time (BUT), Schirmer, and mucus fern tests are used for investigation of DED. However, they are not always reliable and none of them alone is sufficient for the diagnosis (6). It has been revealed that increased tear osmolarity causes the symptoms and signs of DED (7). Recently, increased tear osmolarity has been considered as a potential gold standard for the diagnosis of DED (6,8). Therefore, in this study we aimed to investigate changes of tear osmolarity in patients with GO. BUT test, Schirmer test, and Ocular Surface Disease Index (OSDI) score were also evaluated.

## MATERIALS AND METHODS

Twenty-three patients with GO (GO group) and 25 healthy controls (control group) were enrolled in the study. GO patients were divided into two subgroups as active GO and inactive GO subgroups. Orbital inflammatory activity was evaluated using the guideline of seven-point modified formulation clinical activity score (CAS), as previously described (9). Patients with CAS  $\geq$  3/7 were defined as active GO and those with CAS  $<$  3/7 as inactive GO. Patients with ocular surface disorders, allergic ocular surface disease, pterygium, contact lens wearing, topical anti-glaucomatous drug use, and diseases which can affect ocular surface such as diabetes mellitus, were excluded from the study. All patients were informed about the study procedure and they consented to participate. This study followed the Tenets of the Declaration of Helsinki and it was approved by the Local Ethics Committee.

### *Clinical assesment*

The degree of proptosis was measured by Hertel exophthalmometry, and the palpebral fissure width was assessed with a millimeter ruler.

### *Ocular surface disease index questionnaire*

OSDI questionnaire consisting of 12 questions related with effect of dry eye on vision-related functioning was used to determine OSDI score (10). The questions are asked with reference to a one-week recall period and responses refer to the frequency: never, occasionally, half of the time, most of the time, or all of the time. Average score was calculated.

### *Tear osmolarity*

Tear osmolarity was measured using TearLab Osmolarity System (TearLab™ Corp., San Diego, CA). When the system was ready, the patient was requested to look up, and tear was collected via a handled pen with a chip test card. After the tear-collection process, the pen was placed on the TearLab™ Reader and the results which were displayed on the monitor was recorded as the TO of that eye.

### *Break-up time test*

BUT test was performed after dropping one drop of fluorescein obtained by wetting fluorescein strip (Fluorescein paper, Haag-Streit AG, Koniz, Switzerland) with non-preserved saline to the lower bulbar conjunctiva. After homogeneous fluorescein distribution provided the patient was asked to look straight ahead without blinking. The time between the final blink and the formation of the first dry point was measured using a chronometer and a biomicroscope with a cobalt blue filter. This test was repeated three times, and the results of the three tests were averaged.

### *Schirmer test*

Three minutes after the topical anesthetic was dropped into the eye Schirmer test was performed with 5 x 35 mm strip of Schirmer filter paper (Schirmer tear test, Optitech Eyecare, Allahabad, India). The first 5-mm section of the strip placed in 1/3 of the external fornix. The wet length of the strip measured after 5 minute was accepted as the result of the test.

### *Statistical Analysis*

Statistical analysis was performed using SPSS version 16.0. The distribution of variables was checked by Kolmogorov-Smirnov test. Gender was compared with chi-square test. Student t-test was used to compare other variables between the groups and Mann-Whitney U test was used to compare subgroups. Pearson corre-

**Table 1.** The demographic and clinical characteristics of the groups (mean±SD).

Characteristic	GO group (n:23)	Control group (n:25)	p value
Age (years)	42.4±5.6	40.9±5.9	0.192
Sex (male/female)	8/15	11/14	0.675
Disease duration (years)	2.4±1.1		
Proptosis degree (mm)	20.0±1.6	16.1±1.2	<0.001
Palpebral fissure width (mm)	12.8±1.4	10.1±0.9	<0.001
Tear osmolarity (mOsm/L)	319.0±17.4	307.9±12.7	<0.001
OSDI score	29.0±20.8	13.2±7.8	<0.001
BUT test (second)	6.8±3.7	12.7±1.9	<0.001
Schirmer test (mm)	5.1±2.3	11.4±3.3	<0.001

BUT; Break-up time, GO; Graves ophthalmopathy, OSDI; Ocular Surface Disease Index

lation coefficients were used to evaluate correlations among the variables. Linear regression analysis was performed to investigate the independent predictors for tear osmolarity. Statistical significance was set at  $p < 0.05$ .

## RESULTS

The demographic and clinical parameters of the groups are given in Table 1. The mean disease duration of GO patients was 2.4±1.1 years. There were no significant differences between the groups regarding age and gender (both  $p > 0.05$ ). GO group had significantly higher proptosis degree and palpebral fissure width values than healthy controls as expected (both  $p < 0.001$ ). The GO patients had significantly higher tear osmolarity levels than the healthy controls ( $p < 0.001$ ). In addition, OSDI score, BUT test, and Schirmer test results were significantly different between the groups (all  $p < 0.001$ ). The demographic and clinical parameters of the subgroups

are given in Table 2. The subgroups were significantly different concerning CAS score ( $p < 0.001$ ). Tear osmolarity levels were significantly higher in active GO subgroup than in inactive GO subgroup ( $p = 0.003$ ). The proptosis degree, palpebral fissure width, OSDI score were not significantly different between the subgroups. However, BUT test, and Schirmer test values were significantly different between the subgroups ( $p = 0.046$ ,  $p = 0.009$ , respectively).

Pearson correlation coefficients showed that tear osmolarity levels were significantly correlated with proptosis degree, CAS score, OSDI score, BUT test, and Schirmer test results (Table 3). However, only the CAS score was independently related to tear osmolarity (Beta: 0.603,  $p < 0.001$ ) in the multivariate analysis including proptosis degree, palpebral fissure width, and disease duration (Table 4).

**Table 2.** The demographic and clinical characteristics of the subgroups (mean±SD).

Characteristic	Active GO subgroup (n=10)	Inactive GO subgroup (n=13)	p value
Age (years)	43.3±5.8	41.8±5.4	0.361
Sex (male/female)	3/7	5/8	0.619
Disease duration (years)	2.7±1.2	2.1±1.0	0.09
CAS score	3.2±0.5	1.4±0.7	<0.001
Proptosis degree (mm)	20.2±1.6	19.8±1.4	0.494
Palpebral fissure width (mm)	13.1±1.4	12.7±1.3	0.382
Tear osmolarity (mOsm/L)	327±15.6	312.6±16.3	0.003
OSDI score	30.7±26.8	27.6±15.1	0.646
BUT test (second)	5.5±3.5	7.6±3.2	0.046
Schirmer test (mm)	4.2±2.5	5.9±1.8	0.009

BUT; Break-up time, CAS; clinical activity score, GO; Graves ophthalmopathy, OSDI; Ocular Surface Disease Index

**Table 3.** Correlations between tear osmolarity levels and the variables in the GO patients.

	Tear osmolarity	
	Correlation coefficient (r)	p value
CAS score	.654	<0.001
Proptosis degree	.383	0.009
Palpebral fissure width	.253	0.090
OSDI score	.477	0.001
BUT test	-.485	0.001
Schirmer test	-.397	0.006

BUT; Break-up time, CAS; clinical activity score, GO; Graves ophthalmopathy, OSDI; Ocular Surface Disease Index

## DISCUSSION

Our results displayed that GO patients had significantly higher tear osmolarity levels than healthy controls. In addition, tear osmolarity levels were significantly higher in active GO patients than in inactive GO patients and CAS score was independently related to tear osmolarity. Further, tear osmolarity levels were significantly correlated with proptosis degree, CAS score, OSDI score, BUT test, and Schirmer test results.

Tear hyperosmolarity has been found to have a main pathogenetic role in DED, and it has been enrolled as a part of the definition of DED (9). Tear hyperosmolarity may be caused by aqueous tear deficiency which occur via a decrease in tear secretion because of lacrimal gland disease, or may be caused by tear insufficiency due to an increase in tear film evaporation (10). Bron et al have stated that reduced corneal sensation and loss of the reflex compensatory increase in lacrimal secretion could be the cause of dry eye in GO patients (11). This progressive decrease in lacrimal secretion results in a progressive elevation in tear osmolarity. They described this as a relative aqueous tear deficiency (11). On the other hand, a disturbance in the functions of eyelid may also cause evaporative DED (tear sufficiency). Previous reports have confirmed that a disturbance in blinking, increased proptosis degree, and higher palpebral fissure width in GO patients increases tear evaporation, which elevates tear osmolarity (2-5).

Recently, it has been reported that inflammation has a main role in ocular surface damage in GO patients (12-14). Gupta et al. indicated that GO was a potential reason of inflammatory ocular surface disorder with dry eye symptomatology (13). Luo et al. stated that there might be a link between the hyperosmolar tear film of dry eye and the induction of ocular surface inflammation (15).

**Table 4.** Influence of different factors on tear osmolarity in patients with Graves Ophthalmopathy.

Variables Tear	Osmolarity (dependent variable)	
	Beta	p value
Degree of exophthalmia (mm)	0.190	0.292
Disease duration (years)	0.078	0.583
Palpebral fissure width (mm)	-0.154	0.382
Clinical activity score	0.603	<0.001
R <sup>2</sup>	0.672	

BUT; Break-up time, CAS; clinical activity score, GO; Graves ophthalmopathy, OSDI; Ocular Surface Disease Index

Yoon et al. have found that BUT and Schirmer values significantly raised after steroid treatment in active GO (12). Our results showed that BUT and Schirmer test results were lower in GO patients than healthy controls and were lower in active GO patients than in inactive GO patients. These findings were in accordance with previous studies (3-5,12). We have found only one study (2) in the literature investigating tear osmolarity in patients with GO. In accordance with our results, Iskeleli et al have demonstrated that tear film osmolarity was significantly higher in patients with GO than healthy controls (2). However, to our best knowledge, we are the first to reveal the relationship between the tear osmolarity and GO clinical activity.

In conclusion, we have revealed that GO patients had higher tear osmolarity levels than healthy controls. In addition, there was a relationship between the disease activity and tear osmolarity. Therefore, we suggest that tear osmolarity measurement may be added to other tests for diagnosing dry eye severity in GO and it may be useful to evaluate the disease activity in patients with GO.

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