ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/ophthal.2020-75878

Non-invasive Assessment of Dry Eye Patients: Correlation of Tear Osmolarity, Tear Meniscus Height and Non-invasive Tear Break-up Time with Other Tests

Kuru Göz Hastalarında Noninvaziv Değerlendirme: Gözyaşı Ozmolaritesi, Gözyaşı Menisküs Yüksekliği ve Noninvaziv Gözyaşı Kırılma Zamanının Diğer Testlerle İlişkisi

Azersara Vural KARAKILIÇ[a], Arzu TAŞKIRAN ÇÖMEZ[a]

[a]Department of Ophthalmology, Çanakkale Onsekiz Mart University Faculty of Medicine, Çanakkale, TURKEY

This study was presented as an orally at XII Congress of ISD&DE, 5-7 October 2017, Athens, Greece.
Dr.Azersara Vural Karakilic. Non-invasive Assessment of Dry Eye Patients: Correlation of Tear Osmolarity, Tear Meniscus Height and Non-invasive Tear Breakup Time with Other Tests. Canakkale Onsekiz Mart University, School of Medicine. 2017.

ABSTRACT Objective: To determine the correlation of non-invasive tests with conventional tear function tests in dry eye patients. **Material and Methods:** One hundred and twenty-two eyes of 61 patients over 18 years old who applied to Çanakkale Onsekiz Mart University School of Medicine, Department of Ophthalmology with dry eye were included in the study. After general ophthalmological examination including best corrected visual acuity, biomicroscopic examination, non-invasive methods like Ocular Surface Disease Index (OSDI) scoring, tear osmolarity, non-invasive tear break-up time (NI-TBUT) measurement with Scheimpflug topography, meibomography, and measurement of the lower lid meniscus height (TMH) with optical coherence tomography were performed. After non-invasive tests, conventional tear function tests like Schirmer test, TBUT, cornea and conjunctiva staining were applied respectively. **Results:** A positive correlation was found between NI-TBUT and conventional TBUT ($p<0.01$ Spearman's rho: 0.473). TBUT was found to be positively correlated with Schirmer test and negatively correlated with corneoconjunctival staining ($p<0.01$ Spearman's rho: 0.393, rho:-0.418). Schirmer test results were correlated positively with TMH and negatively correlated with OSDI scoring and corneoconjunctival staining ($p<0.05$ Spearman's rho: 0.181; $p<0.05$ Spearman's rho:-0.214; $p<0.01$ Spearman's rho:-0.394). Tear osmolarity test results and meibomography did not correlate with any test. **Conclusion:** The non-invasive and objective measurement of NI-TBUT may be a better diagnostic modality than TBUT for dry eye patients. Tear osmolarity and meibomography were not significant for diagnosis of early stage dry eye patients.

Keywords: Dry eye syndrome; osmolar concentration; Schirmer test; tear meniscus height; tear osmolarity; tear break-up time; meibomography

ÖZET Amaç: Kuru göz hastalarında, noninvaziv testlerin, konvansiyonel gözyaşı fonksiyon testleri ile korelasyonunu araştırmak. **Gereç ve Yöntemler:** Çanakkale Onsekiz Mart Üniversitesi Tıp Fakültesi Göz Hastalıkları Anabilim Dalına başvuran ve kuru gözü olan 18 yaşından büyük 61 hastanın 122 gözü çalışmaya alındı. Hastalara en iyi düzeltilmiş görme keskinliği ölçümü, biyomikroskobik ve oftalmoskopik muayeneyi içeren genel oftalmolojik muayene sonrasında sırasıyla noninvaziv yöntemler olan, "Ocular Surface Disease Index (OSDI)" anketi, gözyaşı ozmolaritesi ölçümü, Scheimpflug topografi ile noninvaziv gözyaşı kırılma zamanı (Nİ-GKZ), meibomografi ve optik koherens tomografi ile alt kapak gözyaşı menisküs yüksekliği (GMY) ölçüldü. Noninvaziv yöntemler sonrasında sırasıyla geleneksel gözyaşı fonksiyon testleri olan Schirmer testi, GKZ, kornea ve konjonktivanın boyanması yapıldı. **Bulgular:** Nİ-GKZ ile GKZ arasında pozitif korelasyon saptandı ($p<0,01$ Spearman'ın rho: 0,473). GKZ'nin Schirmer testi ile pozitif, korneal boyanma ile negatif korelasyonu olduğu saptandı ($p<0,01$ Spearman'ın rho: 0,393; rho: -0,418). Schirmer testi, GMY ile pozitif, OSDI skoru ve korneokonjonktival boyanma ile negatif korele idi ($p<0,05$ Spearman'ın rho: 0,181; $p<0,05$ Spearman'ın rho: -0,214; $p<0,01$ Spearman'ın rho: -0,394). Gözyaşı ozmolaritesi ve meibomografi testlerinin hiçbir testle korelasyon göstermediği tespit edildi. **Sonuç:** Nİ-GKZ, noninvaziv ve objektif bir ölçüm olması sebebiyle, kuru göz hastalarında GKZ'den daha iyi bir tanısal yöntem olabilir. Gözyaşı ozmolaritesi ölçümü ve meibomografi sonuçları özellikle erken evre kuru göz hastalarının tanısında anlamlı bulunmamıştır.

Anahtar Kelimeler: Kuru göz sendromu; ozmolar konsantrasyon; Schirmer testi; gözyaşı menisküs yüksekliği; gözyaşı ozmolaritesi; gözyaşı kırılma zamanı; meibomografi

According to the International Dry Eye Workshop (DEWS) report in 2017, dry eye is a "multifactorial disease of the ocular surface characterized by loss of homeostasis of the tear film". The etiology includes tear film instability and the disease is accompanied by ocular symptoms affected by hyperosmolarity, ocular surface inflammation and injury, and neurosensorial abnormalities.[1] Studies have reported

Correspondence: Arzu TAŞKIRAN ÇÖMEZ
Department of Ophthalmology, Çanakkale Onsekiz Mart University Faculty of Medicine, Çanakkale, TURKEY/TÜRKİYE
E-mail: arzucomez@yahoo.com

Peer review under responsibility of Turkiye Klinikleri Journal of Ophthalmology.

Received: 29 Apr 2020 ***Received in revised form:*** 11 Aug 2020 ***Accepted:*** 31 Aug 2020 ***Available online:*** 31 Dec 2020

2146-9008 / Copyright © 2021 by Türkiye Klinikleri. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

incidence from 5 to 50% according to age, gender and race.[1-4]

Diagnosis of dry eye disease is made with anamnesis and examination findings, but there is no single gold standard method and diagnosis is only made with a combination of many tests. In recent years, the use of less invasive or even non-invasive methods to research tear film layers have come to the agenda, with these methods revealed to assess the tear film layer as closely as possible to the "physiological" state. Many traditional tests are invasive and this affects the results. Thus, there is a need for easily applicable and high-reliability non-invasive tests for dry eye diagnosis.

A variety of studies researched non-invasive methods such as surveys, tear meniscus height (TMH) and area, non-invasive tear break-up time (NI-TBUT), tear osmolarity and meibomius gland imaging in recent years.[1,5-9]

In our study, we aimed to assess the correlations between non-invasive tests and invasive test results to reveal the place of non-invasive methods for diagnosis of dry eye disease.

MATERIAL AND METHODS

This prospective study received permission from Çanakkale Onsekiz Mart University local ethics committee (number 2011-KAEK-27/2016-E.21549) and written informed consent was obtained from each subject. The study was performed by adherence to the Declaration of Helsinki. The study included 122 eyes of 61 patients aged 18 years and older, with Schirmer test results <10 mm, break-up time score <10 mm and Ocular Surface Disease Index (OSDI) score >13, who signed an informed consent form. The cases were admitted to Çanakkale Onsekiz Mart University Faculty of Medicine, Ophthalmology clinic with complaint of dry eyes (stinging, burning, watering, feeling of foreign body in the eye) and were not using any treatment. Those with active ocular infection or allergies, eyelid deformity or movement disorder, blepharitis and history of lacrimal stenosis surgery and those treated with diuretics, antidepressants, or antihistamine drugs were not included in the study.

After general ophthalmological examination including best corrected visual acuity (BCVA), biomicroscopic examination, patients had the non-invasive methods of OSDI survey, tear osmolarity measurements, NI-TBUT, meibomography and lower lid TMH measurements performed. After non-invasive methods, all patients had the invasive and conventional diagnostic methods of Schirmer test, TBUT, corneal and conjunctival staining applied.

The OSDI survey, which is a 12-question survey assessing ocular irritation symptoms linked to dry eye and functions related to vision, questions ocular symptoms, environmental stimuli and vision-related functions. The subject marks the relevant severity from 0 (never) to 4 (all the time) and total OSDI score is calculated as follows;

OSDI=[(total score for all questions answered) x100]/[(total number of questions answered)x4].

The OSDI score has a maximum value of 100 and a minimum of 0.[10]

For tear osmolarity measurement, a 50-nL tear sample was taken from the lower lid lateral tear meniscus without touching the eye with a tear lab device (TearLab Osmolarity System (TearLab Corporation, San Diego, CA). TMH was measured with an optical coherence tomography (OCT) device (Cirrus HD-OCT, Carl Zeiss Meditec, Dublin, CA) immediately after the patient blinked. The height of the tear pooling on the lower lid was measured without contact and recorded (Figure 1). Before measurement, the patient was asked to look at a target in primary position, with the patient asked to blink before each measurement and three measurements taken for each eye. For measurement, sections were taken at the center of the lower eyelid vertically through the lower cornea. The tear height (μm) was calculated vertically at the point where the lower eyelid and cornea joined. The result was recorded as the mean of three measurements in microns.

The TBUT for the patient was first determined with the non-invasive method. The patients placed their chin and forehead on a Sirius topography (Sirius Scheimpflug Camera System, Schwind, Kleinostheim, Germany) device and were then asked to look in the primary position opposite and recordings were

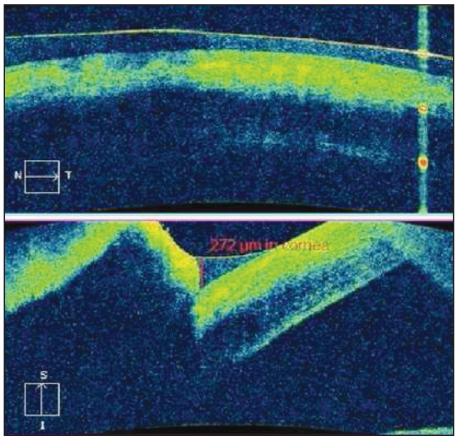

FIGURE 1: Tear meniscus height was measured by optical coherence tomography (OCT) (Cirrus HD-OCT, Carl Zeiss Meditec, Dublin, CA) device.

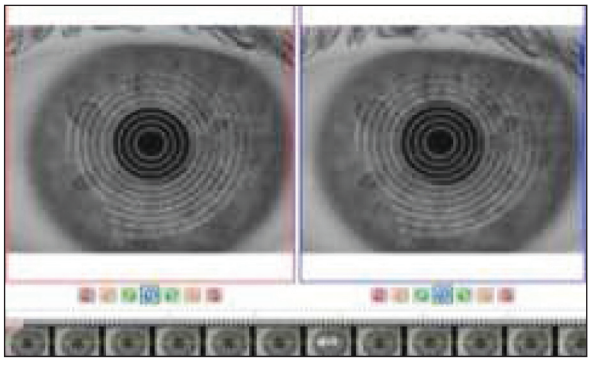

FIGURE 2: The non-invasive tear break-up time measured by Sirius topography (Sirius Scheimpflug Camera System, Schwind, Kleinostheim, Germany) device.

taken with a videokeratoscope. For this test, the shape formed by the lines cutting the eye surface is reflected and the duration until the reflected lines break-up, gives the TBUT (Figure 2). If this duration is less than 10 seconds, it is assessed in favor of dry eye disease.

Meibomius gland imaging was again performed with a Sirius topography device. The patient's lower eyelid was everted and the meibomius glands were imaged with infrared light. The whole of the tarsal region was marked with a program included in the software of the device and the regions of the visible meibomius glands were marked again. The proportion of these two areas to each other was recorded as a percentage (Figure 3).

After the non-invasive tests, topical anesthesia was used for TBUT using fluorescein drops. The patient was requested to blink once and then requested to keep their eyes open. The cornea was viewed with a biomicroscope under cobalt blue light, and the time from the last blink to the first black point forming on the cornea was recorded as tear film break-up time. If this duration is less than 10 seconds, it is assessed in favor of dry eye.

The Schirmer test assesses basal and reflex secretions when topical anesthesia is not administered. Whatman filter paper with 5x35 mm size is placed in the region of the lower eyelid at the junction of 1/3 central and 1/3 outer lines on the lower conjunctival fornix. Five minutes later the amount of wetness is expected to be a minimum of 10 mm.

Then the patients had corneoconjunctival staining score measured. After staining with fluorescein, scoring was placed from 0 to 3 according to the Oxford scale. Oxford scoring was made as follows;

0: No staining, 1: occasional point staining of less than 1/3 of the cornea.

2: Moderate staining between stage 1 and 3, 3: widespread staining involving more than half of the cornea.

In our study, an Oxford score of 1 and above was accepted as abnormal.

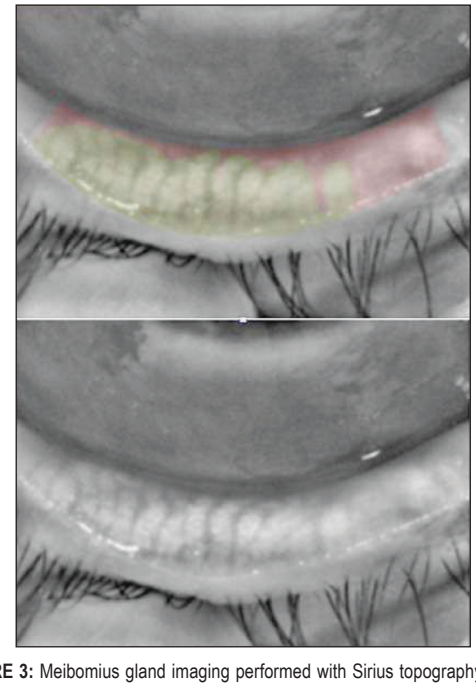

FIGURE 3: Meibomius gland imaging performed with Sirius topography (Sirius Scheimpflug Camera System, Schwind, Kleinostheim, Germany) device.

STATISTICAL ANALYSIS

The data obtained in this research were analyzed with the SPSS 20.0 statistical program. Variables are shown as mean±standard deviations. Comparisons and correlations between tear osmolarity measurement, meibomian gland imaging, tear meniscus measurement with OCT and TBUT determined with a keratoscope and the conventional diagnostic methods of the Schirmer test, corneal fluorescein staining, and TBUT with fluorescein were assessed. $p<0.05$ was accepted as statistically significant.

RESULTS

The study included 50 (82%) females and 11 (18%) males for a total of 122 eyes of 61 dry eye patients. The mean age of the patients was 51.5±12.8 years. For all tests, there were no significant differences between the right and left eyes. The results of parameters measured are shown in Table 1.

CORRELATIONS

Ocular Surface Disease Index

OSDI survey results were negatively correlated with the Schirmer test with no correlation identified with any other test (Spearman's rho:-0.214, $p<0.05$). The mathematical absolute average of the Spearman's rho correlation values for the OSDI test was calculated as 0.095.

Tear Osmolarity Test Results

The mean tear osmolarity of eyes included in our study was found to be 286.5±24.6 mOsm/L. Tear osmolarity was not correlated with any test. The mathematic absolute mean of the Spearman's rho correlation value for osmolarity measurement was calculated as 0.107.

TABLE 1: Results of parameter measurements.

	Mean	Minimum	Maximum
NI-TBUT (s)	5.9	1	9
TBUT (s)	6.4	1	9
Schirmer (mm)	7.6	2	10
Tear osmolarity (mOsm/L)	286.5	275	302
OSDI score	50.76	12	83
TMH (μ)	136.7	65	302
Meibomography (%)	50.1	27	82

NI-TBUT: Non-invasive tear break-up time; TBUT: Tear break-up time; s: Second; OSDI: Ocular Surface Disease Index Score; TMH: Tear meniscus height.

Tear Break-Up Time Assessment Results

The mean conventional TBUT of eyes included in the study was 6.4±2.7 seconds. The TBUT was positively correlated with NI-TBUT, Schirmer test and corneal staining (Oxford score) (Spearman's rho: 0.473, $p<0.01$; rho: 0.393, $p<0.01$; rho: 0.418, $p<0.01$, respectively). The mathematical absolute mean of the Spearman's rho correlation value for invasive TBUT was calculated as 0.248.

Non-invasive Tear Break-up Time Assessment Results

The mean NI-TBUT for eyes included in the study was 5.9±3.0 seconds, and NI-TBUT was positively correlated only with TBUT (Spearman's rho: 0.473, $p<0.01$). The mathematical absolute mean of the Spearman's rho correlation values for invasive TBUT was calculated as 0.188.

Tear Meniscus Height Measurement with Optical Coherence Tomography

The mean TMH measured with OCT-anterior segment module was 136.7±44.5 microns. The TMH values were positively correlated only with the Schirmer test (Spearman's rho: 0.181, $p<0.05$). The lowest meniscus height was 65 microns while the highest was 302 microns. The mathematical absolute mean of the Spearman's rho correlation values for mean TMH was calculated as 0.104.

Meibomography Assessment Results

The mean meibomian gland percentage of eyes included in our study was 50.1%±13.2%. This percentage was not correlated with other tests and the mathematical absolute mean for Spearman's rho correlation values was calculated as 0.100. The lowest percentage was 27% and highest percentage was 82%.

Schirmer Test Assessment Results

The mean Schirmer test value for eyes included in the study was found to be 7.6±2.7 mm. The Schirmer test was positively correlated with invasive TBUT and mean TMH (Spearman's rho: 0.393, $p<0.01$; rho: 0.181, $p<0.05$, respectively).

As expected, the Schirmer test showed a negative correlation with corneal staining and OSDI (Spearman's rho: -0.394, p<0.01; rho: -0.214, p<0.05, respectively). The mathematical absolute mean of the Spearman's rho correlation values for the Schirmer test was calculated as 0.242.

Ocular Surface Staining Assessment Results

Of the 61 patients included in the study, 120 eyes of 60 patients had corneoconjunctival staining performed. One patient stated that she had staining performed before in another clinic and did not wish to do it again due to feeling pain. Staining patterns were investigated according to the Oxford scale and patients were assessed from zero to four for clinical staging. Accordingly, 56 eyes (40.3%) were "stage 0"; 42 eyes (30.2%) were "stage 1"; 12 eyes (8.6%) were "stage 2"; 7 eyes (5%) were "stage 3" and 3 eyes (2.2%) were "stage 4". Corneal staining showed a negative correlation with invasive TBUT and Schirmer test (Spearman's rho: -0.418, p<0.01; rho: -0.394, p<0.01, respectively). The mathematical absolute mean of the Spearman's rho correlation values for corneal staining was calculated as 0.227.

DISCUSSION

The incidence of dry eye syndrome has reported rates of 5% to 50% depending on age, gender and race.[1-3] DEWS report suggests that the presence of dry eye symptoms is needed to confirm dry eye diagnosis.[2] Although dry eye symptoms are commonly observed, there is frequently an inconsistency between clinical findings and severity of symptoms causing difficulties in the diagnosis, treatment and monitoring of the disease.[11,12]

The literature indicates that the symptoms and history of disease are important components, and symptoms should generally be assessed in combination with objective tests.[1,2] These tests should be performed in a standardized manner and with a defined pattern in terms of obtaining accurate results, making correct diagnoses and assessing the efficacy of treatment.

In the current study, we first applied the OSDI survey to all patients. This test is important as it considers the patient's subjective complaints along with environmental factors.[5,6,13] The mean OSDI score in our study was 50.76. A study by Schiffman et al. researching the reliability and validity of the OSDI survey reported the OSDI score was 10 or less for normal individuals, >21 for patients with mild-moderate dry eyes, and 36 and above for patients with severely dry eyes.[10] Another study assessing the correlation of the OSDI score with other tests found an OSDI score >15 had 79.5% sensitivity and 70% specificity for dry eyes.[8] The positive correlations of OSDI score with ocular staining score and tear osmolarity and negative correlations with Schirmer and TBUT in our study are expected results due to the pathophysiology of dry eye disease. Similar to our results, Schiffman and Tuisku et al. identified negative correlations between OSDI and the Schirmer test.[10,14] Schmidl et al., reported a negative correlation between OSDI survey and TMH.[15]

Lemp et al., in a study in 2011 reported tear osmolarity had 72.8% sensitivity and 92% specificity for dry eye diagnosis. The same study reported the specificity of corneal staining was 54%, meibomian gland loss was 60.3%, TBUT was 45.3% and Schirmer test was 50.7%.[9]

In the literature, the threshold value for tear osmolarity is reported from 305 to 316 mOsm/L.[16,17] A review related to osmolarity published by Potvin et al. in 2015 investigated 163 studies and determined 32% had high quality in terms of sample size, randomization and control group.[17] Of the studies included in the review, 73% reported that tear osmolarity had positive effect on dry eye diagnosis, 17% reported that it had no significant effect on diagnosis and 10% stated it had a negative effect on diagnosis.[17] Some studies reported that tear osmolarity is affected mostly by the severity of the disease.[11,16]

In our study, tear osmolarity was minimum 275, maximum 302 and mean 286.5 mOsm/L, contrary to the means in these studies. Due to these results, we tested our osmolarity device and test solutions between cases with solutions with high and low osmolarities to be sure that our device was working correctly. We also identified tear osmolarity was not correlated with any other test. We think this result may be due to our dry

eye patients having mild and moderate severity. Some studies have reported overlap between osmolarity measurement results of dry eye patients and normal individuals. They reported this result may be a limitation for the use of the osmolarity test for dry eye diagnosis.[18,19] The correlation between tear osmolarity and other diagnostic tests strengthens as the severity of dry eye increases.[9] Another review related to tear osmolarity reported a weak correlation between tear osmolarity and other tear function tests, similar to our results.[17]

In the literature, there are studies showing tear osmolarity is high for dry eye patients, while there are also studies showing normal or hypoosmolarity.[9,11,20-24] We associate this result with the possibility of different osmolarity values of the tear as being hypoosmolar, isoosmolar or hyperosmolar, which is presented in different subtypes of dry eyes with different pathophysiological mechanisms.

We did not identify any correlation between tear osmolarity and symptoms, corneal staining and other objective tests. Studies by Messmer et al. and Yang et al., also reported no correlation between tear osmolarity and symptoms and other objective tests, similar to our study.[18,25]

The oldest method used for dry eye diagnosis, the Schirmer test, showed positive correlations with TBUT and TMH measured with OCT. The Schirmer test also showed negative correlations with corneal staining and OSDI. A study by Kim et al. identified a strong correlation between the Schirmer test and tear osmolarity, TBUT, Rose Bengal and Lissamine green staining and the McMonnies test score for patients with Sjögren syndrome.[26]

In our study, we identified that the test with most correlations to other tests was the Schirmer test. Contrary to our result, in a study evaluating the correlations between dry eye tests, Sullivan et al. reported they did not identify any correlation between the Schirmer test with OSDI, tear osmolarity, TBUT and corneal staining.[7]

The Oxford staging scale frequently used for corneoconjunctival staining score is a staging system evaluating dry eye. In our study, 120 eyes of 60 patients, out of 61, had corneoconjunctival staining patterns assessed according to the Oxford scale with patients evaluated from zero to four. According to these results, the majority of our patients were revealed to be early stage dry eye patients. In spite of this, corneoconjunctival staining scores in our study showed a negative correlations with TBUT and Schirmer test, as expected.

In dry eye patients, the destabilized tears increase the contact between the cornea and air in the advanced period and cause epithelial defects. Fluorescein stains the cavities between cells, while sturdy epithelium normally prevents passage of the water-soluble fluorescein into the stroma.[27] As a result, corneal staining is not sufficient alone to diagnose dry eyes especially in the early stage.[20] Sullivan et al. reported no correlation between corneal staining and other dry eye tests.[7] Staining alone may be insufficient to differentiate people with dry eyes from healthy individuals, especially in the early stages of dry eye.

In our study, the mean TBUT measurement was 6.6±2.7 seconds, and it is found to show positive correlations with NI-TBUT, the Schirmer test and corneal staining. We think NI-TBUT can be applied instead of TBUT due to this positive correlation, the ease of application, and allowing monitoring dry eye with a quantitative value.

A study researching the epidemiology of dry eye revealed that, dry eye progressing with shortened TBUT is more common compared to other dry eye types.[28] This result reveals the importance of TBUT in diagnosis.

As the most encountered type of dry eye is mainly occurred due to increased evaporation, the Asia Dry Eye Society consensus published in 2017 stated that dry eye may be diagnosed only by assessing symptoms and with shortened TBUT.[29] The first non-invasive approach for the diagnosis of dry eye was initially proposed by Lamble et al. in 1976 by projecting a grid pattern onto the tear film surface of rabbit corneas and observing the distortion after blinking.[30] In our study NI-TBUT was measured with a modified topographic system, and NI-TBUT was found to correlate with conventional TBUT results. There was no correlation between NI-TBUT and TMH measured with OCT. During NI-TBUT measurement, patients were requested to blink their eyes for a time. There are studies showing a changing effect on tear dynamics due to de-

layed blinking and reflex tearing that occurs during this time.[31,32] From this perspective, we think the lack of correlation between TMH measured with OCT and NI-TBUT may be related to delayed blinking and reflex tearing.

In the current study, TMH was found to be positively correlated only with Schirmer test. The positive correlation between these two tests assessing tear amounts is an expected result, while there may be false positive results from the Schirmer test due to being an invasive method causing reflex tear secretion. A study assessing the correlation between objective and subjective dry eye disease tests identified a positive correlation between TMH and TBUT, OSDI and corneal staining.[33] Another study researching the correlation between TMH and conventional dry eye tests found that TMH was correlated with the Schirmer test but not correlated with OSDI.[34] Another study found the sensitivity and specificity of TMH measurement with OCT were 80.56% and 89.33%, respectively, and identified the expected negative correlation between TMH and OSDI.[35] Oguz et al., in their study evaluating the correlation of TMH and tear meniscus curve radius, reported a mean TMH value of 190±90 microns which is measured by a slit lamp equipped with a micrometer without instillation of flourescein. The mean TMH in the current study was 136.7±44.5 microns as mesured by OCT. The tracking system in OCT may be the reason for the difference, as OCT allowed measuring TMH even at smaller volumes where measurement with micrometer could not be facilitated due to nonvisible tear meniscus in some patients.[36] Infrared meibomography observes normal meibomian glands as grape-like clusters providing hypoillumination, while the ductus and tarsus below are hyperilluminous.[37,38]

The meiboscore was defined by Arita et al. in 2008 and is based on showing the partial presence or total absence of the meibomius gland. The lost area is given as a proportion of the total eyelid area to produce a numerical score.[39] Assessment is (0): partial gland or no loss of gland on the eyelid, (1): glands are present on <33% of eyelid area, (2): glands are present in 33-66% of the eyelid, (3): glands are present in >66% of the assessed area.[39]

This scoring system is noteworthy for ensuring both image analysis and data digitization in a single value and shows variations in the meibomian gland structure.[39] In our study, the meibomian gland loss was mean 50.1% for the eyes included in our study. This rate is very high for our patients who were mainly in the early stage of dry eye. In the literature there is very little data related to the meiboscore. Meibomian gland investigation in healthy young people identified that, 29% of individuals had ≥20% gland atrophy. Only 13% of participants had atrophy score of 0, with 87% of participants reported to have atrophy from 1 to 100%.[40]

In our study, we did not identify any correlation between meibomian gland loss and all other tear function tests. Sullivan et al., similarly, reported no correlation between meibomian gland assessment and other objective tests as in a study by Meadows et al.[7,41]

CONCLUSION

Though the pathogenesis, classification and features of dry eye syndrome are very well known, there is no consensus about which reproducible, easy and objective method has sufficient specificity and sensitivity to use for diagnosis. While some of the tests in our study were correlated, the majority were not. These results are consistent with the possibility of reflecting different subtypes of dry dye disease with different mechanisms and each clinical finding is recommended as they provide different information about the state of the ocular surface.

Among all tests, the Schirmer test had positive correlations with TBUT and TMH, and negative correlations with corneoconjunctival staining and the OSDI survey. As NI-TBUT is correlated with TBUT, it may be used instead of TBUT in appropriate patients. No test was correlated with osmolarity. TMH may be chosen in terms of non-invasive approaches, though there is no threshold value for differentiating normal and dry eyes with consensus in the literature so we think it is more valuable for treatment monitoring rather than having diagnostic importance. Meibomian gland assessment is valuable in terms of being non-invasive, but is not correlated with any tear function test. Considering dry eye is a chronic and progressive disease, all test results should be assessed together with clinical situation.

Source of Finance

The study is supported by Canakkale Onsekiz Mart University, Scientific Research Project Center, Project number: TTU-2016-1008

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Arzu Taşkıran Çömez, Azersara Vural Karakılıç;* ***Design:*** *Arzu Taşkıran Çömez, Azersara Vural Karakılıç;* ***Control/Supervision:*** *Arzu Taşkıran Çömez, Azersara Vural Karakılıç;* ***Data Collection and/or Processing:*** *Azersara Vural Karakılıç, Arzu Taşkıran Çömez;* ***Analysis and/or Interpretation:*** *Azersara Vural Karakılıç, Arzu Taşkıran Çömez;* ***Literature Review:*** *Azersara Vural Karakılıç, Arzu Taşkıran Çömez;* ***Writing the Article:*** *Azersara Vural Karakılıç, Arzu Taşkıran Çömez;* ***Critical Review:*** *Arzu Taşkıran Çömez;* ***References and Fundings:*** *Arzu Taşkıran Çömez;* ***Materials:*** *Arzu Taşkıran Çömez, Azersara Vural Karakılıç.*

REFERENCES

1. Nelson JD, Craig JP, Akpek EK, Azar DT, Belmonte C, Bron AJ, et al. TFOS DEWS II Introduction. Ocul Surf. 2017;15(3):269-75.[Crossref] [PubMed]
2. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf. 2007;5(2):75-92.[Crossref] [PubMed]
3. Moss SE, Klein R, Klein BE. Prevalence of and risk factors for dry eye syndrome. Arch Ophthalmol. 2000;118(9):1264-8.[Crossref] [PubMed]
4. Lee AJ, Lee J, Saw SM, Gazzard G, Koh D, Widjaja D, et al. Prevalence and risk factors associated with dry eye symptoms: a population based study in Indonesia. Br J Ophthalmol. 2002;86(12):1347-51.[Crossref] [PubMed] [PMC]
5. Versura P, Cellini M, Torreggiani A, Profazio V, Bernabini B, Caramazza R. Dryness symptoms, diagnostic protocol and therapeutic management: a report on 1,200 patients. Ophthalmic Res. 2001;33(4):221-7.[Crossref] [PubMed]
6. Bayhan HA, Gürdal C, Takmaz T, Can İ. [Comparison of lissamine green and rose bengal in dry eye diagnosis and correlation between patient symptoms and clinical tests]. Turk J Ophthalmol 2010;40(1):29-33.[Link]
7. Sullivan BD, Crews LA, Messmer EM, Foulks GN, Nichols KK, Baenninger P, et al. Correlations between commonly used objective signs and symptoms for the diagnosis of dry eye disease: clinical implications. Acta Ophthalmol. 2014;92(2):161-6.[Crossref] [PubMed]
8. Taşkıran Çömez A, Kömür B, Şanal E, Tufan HA. [The relationship between tear osmolarity, Ocular Surface Disease Index© and other tear function tests]. Turkiye Klinikleri J Med Sci. 2013;33(2):455-63.[Crossref]
9. Lemp MA, Bron AJ, Baudouin C, Benítez Del Castillo JM, Geffen D, Tauber J, et al. Tear osmolarity in the diagnosis and management of dry eye disease. Am J Ophthalmol. 2011;151(5):792-8.[Crossref] [PubMed]
10. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. Arch Ophthalmol. 2000;118(5):615-21.[Crossref] [PubMed]
11. Sullivan BD, Whitmer D, Nichols KK, Tomlinson A, Foulks GN, Geerling G, et al. An objective approach to dry eye disease severity. Invest Ophthalmol Vis Sci. 2010;51(12):6125-30.[Crossref] [PubMed]
12. Fuentes-Páez G, Herreras JM, Cordero Y, Almaraz A, González MJ, Calonge M. [Lack of concordance between dry eye syndrome questionnaires and diagnostic tests]. Arch Soc Esp Oftalmol. 2011;86(1):3-7.[Crossref] [PubMed]
13. Karalezli A, Borazan M, Küçükerdönmez C, Akova YA. [Comparison of the effect of different concentrations of topical sodium hyaluronate eye drops for the treatment of dry eye]. Turkiye Klinikleri J Ophthalmol. 2010;19(2):78-83.[Link]
14. Tuisku IS, Konttinen YT, Konttinen LM, Tervo TM. Alterations in corneal sensitivity and nerve morphology in patients with primary Sjögren's syndrome. Exp Eye Res. 2008;86(6):879-85.[Crossref] [PubMed]
15. Schmidl D, Witkowska KJ, Kaya S, Baar C, Faatz H, Nepp J, et al. The association between subjective and objective parameters for the assessment of dry-eye syndrome. Invest Ophthalmol Vis Sci. 2015;56(3):1467-72.[Crossref] [PubMed]
16. Jacobi C, Jacobi A, Kruse FE, Cursiefen C. Tear film osmolarity measurements in dry eye disease using electrical impedance technology. Cornea. 2011;30(12):1289-92.[Crossref] [PubMed]
17. Potvin R, Makari S, Rapuano CJ. Tear film osmolarity and dry eye disease: a review of the literature. Clin Ophthalmol. 2015;9:2039-47.[Crossref] [PubMed] [PMC]
18. Messmer EM, Bulgen M, Kampik A. Hyperosmolarity of the tear film in dry eye syndrome. Dev Ophthalmol. 2010;45:129-38.[Crossref] [PubMed]
19. Szalai E, Berta A, Szekanecz Z, Szûcs G, Módis L Jr. Evaluation of tear osmolarity in non-Sjögren and Sjögren syndrome dry eye patients with the TearLab system. Cornea. 2012;31(8):867-71.[Crossref] [PubMed]
20. Sullivan BD, Crews LA, Sönmez B, de la Paz MF, Comert E, Charoenrook V, et al. Clinical utility of objective tests for dry eye disease: variability over time and implications for clinical trials and disease management. Cornea. 2012;31(9):1000-8.[Crossref] [PubMed]
21. Walsh NP, Fortes MB, Raymond-Barker P, Bishop C, Owen J, Tye E, et al. Is whole-body hydration an important consideration in dry eye? Invest Ophthalmol Vis Sci. 2012;53(10):6622-7.[Crossref] [PubMed]
22. Bunya VY, Langelier N, Chen S, Pistilli M, Vivino FB, Massaro-Giordano G. Tear osmolarity in Sjögren syndrome. Cornea. 2013;32(7):922-7.[Crossref] [PubMed] [PMC]
23. Di Tommaso C, Valamanesh F, Miller F, Furrer P, Rodriguez-Aller M, Behar-Cohen F, et al. A novel cyclosporin a aqueous formulation for dry eye treatment: in vitro and in vivo evaluation. Invest Ophthalmol Vis Sci. 2012;53(4):2292-9.[Crossref] [PubMed]
24. Cho KJ, Mok JW, Choi MY, Kim JY, Joo CK. Changes in corneal sensation and ocular surface in patients with asymmetrical keratoconus. Cornea. 2013;32(2):205-10.[Crossref] [PubMed]
25. Yang Y, Abrams M, Garner W, Rinehart M, Senic BP, Shimada H, et al. An exploration of the relationships between tear osmolarity and other measures of dry eye signs and symptoms. Invest Ophthalmol Vis Sci. 2012;53:548.[Link]

26. Kim M, Kim HS, Na KS. Correlation between tear osmolarity and other ocular surface parameters in primary Sjögren's syndrome. Korean J Ophthalmol. 2017;31(1):25-31. [Crossref] [PubMed] [PMC]
27. Yokoi N, Takehisa Y, Kinoshita S. Correlation of tear lipid layer interference patterns with the diagnosis and severity of dry eye. Am J Ophthalmol. 1996;122(6):818-24.[Crossref] [PubMed]
28. Tong L, Chaurasia SS, Mehta JS, Beuerman RW. Screening for meibomian gland disease: its relation to dry eye subtypes and symptoms in a tertiary referral clinic in singapore. Invest Ophthalmol Vis Sci. 2010;51(7):3449-54. [Crossref] [PubMed]
29. Tsubota K, Yokoi N, Shimazaki J, Watanabe H, Dogru M, Yamada M, et al; Asia Dry Eye Society. New perspectives on dry eye definition and diagnosis: a consensus report by the Asia Dry Eye Society. Ocul Surf. 2017;15(1):65-76.[PubMed]
30. Lamble JW, Gilbert D, Ashford JJ. The break-up time of artificial pre-ocular films on the rabbit cornea. J Pharm Pharmacol. 1976;28(5): 450-1. [Crossref] [PubMed]
31. Gumus K, Crockett CH, Rao K, Yeu E, Weikert MP, Shirayama M, et al. Noninvasive assessment of tear stability with the tear stability analysis system in tear dysfunction patients. Invest Ophthalmol Vis Sci. 2011;52(1):456-61.[Crossref] [PubMed] [PMC]
32. Best N, Drury L, Wolffsohn JS. Clinical evaluation of the Oculus Keratograph. Cont Lens Anterior Eye. 2012;35(4):171-4.[Crossref] [PubMed]
33. Nichols KK, Nichols JJ, Mitchell GL. The lack of association between signs and symptoms in patients with dry eye disease. Cornea. 2004;23(8):762-70.[Crossref] [PubMed]
34. Savini G, Barboni P, Zanini M. Tear meniscus evaluation by optical coherence tomography. Ophthalmic Surg Lasers Imaging. 2006;37(2):112-8. [Crossref] [PubMed]
35. Czajkowski G, Kaluzny BJ, Laudencka A, Malukiewicz G, Kaluzny JJ. Tear meniscus measurement by spectral optical coherence tomography. Optom Vis Sci. 2012;89(3):336-42.[Crossref] [PubMed]
36. Oguz H, Yokoi N, Kinoshita S. The height and radius of the tear meniscus and methods for examining these parameters. Cornea. 2000;19(4):497-500.[Crossref] [PubMed]
37. Tomlinson A, Bron AJ, Korb DR, Amano S, Paugh JR, Pearce EI, et al. The international workshop on meibomian gland dysfunction: report of the diagnosis subcommittee. Invest Ophthalmol Vis Sci. 2011;52(4):2006-49.[Crossref] [PubMed] [PMC]
38. Jester JV, Rife L, Nii D, Luttrull JK, Wilson L, Smith RE. In vivo biomicroscopy and photography of meibomian glands in a rabbit model of meibomian gland dysfunction. Invest Ophthalmol Vis Sci. 1982;22(5):660-7. [PubMed]
39. Arita R, Itoh K, Maeda S, Maeda K, Furuta A, Fukuoka S, et al. Proposed diagnostic criteria for obstructive meibomian gland dysfunction. Ophthalmology. 2009;116(11):2058-63.[Crossref] [PubMed]
40. Gupta PK, Stevens MN, Kashyap N, Priestley Y. Prevalence of meibomian gland atrophy in a pediatric population. Cornea. 2018;37(4): 426-30. [Crossref] [PubMed] [PMC]
41. Meadows JF, Ramamoorthy P, Nichols JJ, Nichols KK. Development of the 4-3-2-1 meibum expressibility scale. Eye Contact Lens. 2012;38(2):86-92.[Crossref] [PubMed]