The Association Between Subjective and Objective Parameters for the Assessment of Dry-Eye Syndrome

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PURPOSE. The aim of the present study was to evaluate the association between symptoms and different clinical signs in patients with dry-eye syndrome (DES).

METHODS. Fifty-two patients with DES were included in the present cross-sectional study. For assessment of symptoms, the Ocular Surface Disease Index (OSDI) was used. Clinical parameters included measurement of tear break up time (BUT), corneal fluorescein staining, tear osmolarity, and ocular scattering index (OSI). Tear film thickness (TFT) was assessed using a custom-built optical coherence tomography (OCT) system with an axial resolution of 1.2 μm. In addition, impression cytology was performed. Correlation coefficients were calculated using linear regression analysis.

RESULTS. The mean OSDI in the present study population was 28.9 ± 17.6, the mean TFT was 4.1 ± 1.3 μm. A significant negative correlation was found between OSDI and TFT (r = −0.54, P = 0.01). Tear film thickness correlated positively with BUT (r = 0.55, P = 0.01), but with no other signs of DES. No association was found between OSDI and the other evaluated signs.

CONCLUSIONS. The study population mainly comprised of patients with mild to moderate DES. Tear film thickness as measured with a custom-built OCT device correlated with subjective symptoms in these patients. In agreement with previous data, the association between other signs and symptoms was weak in the present study. Measurement of TFT with OCT may become a valuable tool in the management of DES patients. (ClinicalTrials.gov number, NCT01753687.)

Keywords: dry-eye syndrome, optical coherence tomography, tear film thickness, ocular surface disease index, tear break up time, corneal fluorescein staining, objective scattering index, tear osmolarity, impression cytology

Dry-eye syndrome (DES) is a highly prevalent condition, especially in the elderly, affecting up to 20% of adults aged 45 years or older.1–3 It is defined as a multifactorial disease of the tears and ocular surface leading to symptoms of discomfort, visual impairment, and instability of the tear film with potential damage to the ocular surface. In addition, DES comes with increased osmolarity of the tear film and ocular surface inflammation.4

Although a wide array of techniques has been used to diagnose and monitor DES, no gold standard for a uniform set of criteria has been established. The Dry Eye Workshop 2007 (DEWS) suggested the use of symptom questionnaires, ocular surface staining, determination of tear break up time (BUT), the Schirmer I test, and measurement of tear film osmolarity for screening and follow-up.5 Even though all of these methods provide relatively good specificity for DES, sensitivity for some methods seems to be relatively low.6,7 The correlation between most of these parameters is weak, especially between subjective assessments and objective methods.8,9 Therefore, in most DES patients a variety of methods is used for diagnosis and follow-up of the disease.9,10

The authors of the DEWS state that newly developed noninvasive imaging techniques such as optical coherence tomography (OCT) of the ocular surface might be promising approaches.5 We recently developed an ultrahigh-resolution Fourier-domain (FD) OCT system that provides a resolution as high as 1.2 μm in tissue for the measurement of tear film thickness (TFT).11,12 Due to its excellent reproducibility and the noninvasive character of the measurement, it might be a valuable tool in the assessment of DES.

The aim of the present cross-sectional study was to evaluate the association between symptoms and different clinical signs in patients with DES. The Ocular Surface Disease Index (OSDI) was used for determination of the subjective severity of DES. These results were compared with established methods such as determination of BUT, fluorescein staining, tear osmolarity, and impression cytology. Further, we also applied new methods such as measurement of TFT using the custom-built OCT and the objective scattering index (OSI).
MATERIALS AND METHODS

Patients

The present study was performed in adherence to the Declaration of Helsinki and the Good Clinical Practice (GCP) guidelines of the European Union. The study protocol was approved by the ethics committee of the Medical University of Vienna. After written informed consent was obtained, 52 patients with DES were included.

During the 4 weeks before the study day, a screening examination was performed, which included recording of medical history, measurement of vital signs, a pregnancy test in women of childbearing potential, determination of best corrected visual acuity (BCVA), and a full ophthalmologic examination. The inclusion criteria with regard to severity of DES were set wide to allow for meaningful correlation between signs and symptoms. Patients had to have a history of DES for at least 3 months and at least two symptoms of DES (foreign body sensation, burning, photophobia, blurred vision, pain, itching) and/or BUT less than 10 seconds, which is defined as the cut-off between healthy subjects and patients with DES by the DEWS. Exclusion criteria were: wearing of contact lenses, treatment with corticosteroids, or any ophthalmic drug except topical lubricants in the 4 weeks preceding the study, or glaucoma, Sjögren’s syndrome, or Stevens-Johnson syndrome. Further exclusion criteria were intake of dietary supplements in the 3 months preceding the study or the presence of other systemic or ocular conditions, which would interfere with the aim of the study as judged by the investigator. Patients had to abstain from administration of topical lubricants in the 24 hours before the screening examination as well as 24 hours before the study day.

Methods

Ocular Surface Disease Index (OSDI). Symptoms of dry eye were assessed using the OSDI, which was developed by the Outcomes Research Group at Allergan, Inc. (Irvine, CA, USA). The questionnaire that underlies the OSDI is specifically designed for patients with DES and asks patients about the frequency of specific symptoms and their impact on vision-related functioning. The score reaches from 0 to 100 points. A value greater than 12 points is defined as the cut-off for having ocular surface disease.

Best Corrected Visual Acuity. Measurement of BCVA was performed using Early Treatment of Diabetic Retinopathy Study (ETDRS) charts.

Measurement of Tear Film Thickness Using OCT. We used a custom-built OCT system for TFT measurements that has been described in detail elsewhere. The light source (Ti:sapphire laser, Integral OCT; Femtolasers Produktions GmbH, Vienna, Austria) has a bandwidth of 170-nm half maximum (FWHM) at a central wavelength of 800 nm, which results in a theoretical axial resolution of 1.2 μm in the tissue of the cornea. The transverse resolution of the employed OCT system is 21 μm at the front corneal surface. The power of the incident light focused onto the cornea was set to 600 μW, which is more than 10 times below the maximum permissible exposure (MPE) specified by the American National Standards Institute and International Electrotechnical Commission 60825-1. For the present experiments, a high-speed charged-coupled device camera (e2v EM4CL 2014; Aviva, Essex, UK) was operated at an acquisition rate of 45 kHz. The light-delivery system of the sample arm was mounted on a modified slit-lamp headrest to minimize head movements and to allow precise alignment of the probe beam onto the patient’s eye. Patients had to look onto an internal fixation target and to blink freely during the alignment procedure, which took approximately 10 seconds. Afterwards, patients were advised to blink once and the measurement started immediately after opening of the eyes. Three volumes with a size of 4 mm × 4 mm × 1 mm (horizontal × vertical × depth) were acquired within 3 seconds, each containing 512 × 128 × 1024 voxels. For calculation of central TFT, in each volume the 15 horizontal frames above the central specular reflex of the probe beam at the apex of the cornea were post processed. The TFT value was determined as the mean of the thickness values for the last two recorded volumes, while the first volume was discarded due to instability of the tear film shortly after blinking.

Objective Scattering Index (OSI). Scattering of the tear film was measured noninvasively with the commercially available Optical Quality Analysis System (OQAS; Visometrics, Terrassa, Spain). In principle, a collimated beam with a beam diameter of approximately 1 mm realized with a 780-nm laser is imaged on the retina. The size and the shape of the light spot (light passes twice through ocular media, after retinal reflection) is then analyzed by the OQAS software. Based on this data, the OSI (objective scattering index) is calculated. Given that changes in the tear film are also reflected in the image produced on the retina, the OSI can be used as a measure of tear film quality. The measurement took 20 seconds during which the patients were instructed not to blink.

Tear Film Osmolarity. Tear film osmolarity was measured with a commercially available instrument (TearLab; OcuSens, Inc., San Diego, CA, USA). The TearLab technology uses a novel approach that concentrates laboratory functions on a single chip requiring less than 50 nL of tear fluid in order to measure tear osmolarity. The system uses a handheld pen on which the ophthalmologist places the laboratory chip test card. Then, the tear sample is collected minimally invasive from the lower outer tear meniscus. Special attention was paid to not induce reflex tearing.

Tear Break up Time (BUT). Tear break up time was measured following the guidelines published in the Report of the International Dry Eye Work Shop (DEWS) 2007. Briefly, 5 μL sodium fluorescein drops (Minims-Fluorescein Sodium 2.0%; Chauvin Pharmaceuticals Ltd., Surrey, UK) were applied from the lower outer tear meniscus. Special attention was paid to not induce reflex tearing.

Staining of the Cornea With Fluorescein. Fluorescein staining of the cornea was performed using fluorescein drops (Minims-Fluorescein Sodium 2.0%; Chauvin Pharmaceuticals Ltd.) to detect corneal damage. The cornea was divided into five regions (central, inferior, superior, nasal, temporal) and each region was graded from 0 to 4 in 0.5 steps as described in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study and recommended by the International Dry Eye Workshop (DEWS) 2007.

Impression Cytology. After topical anesthesia of the eye by means of oxybuprocainhydrochloride, cellulose acetate filter material was placed on the bulbar conjunctival surfaces. Samples were obtained at the 12:00 and 6:00 o’clock position in each eye. Staining was performed as a combination of Gill’s modified Papanicolaou stain and periodic acid-Schiff (PAS) reaction as described in detail by Tseng and Haller-Schober et
Each sample was evaluated by three different examiners (DS, KJW, and CB) according to the score published by Haller-Schober et al.20 Each score includes evaluation of the epithelial cell sheet, degree of squamous metaplasia, degree of keratinization, nuclear changes frequency and type, goblet cell density and morphology, mucus amount, and morphology and inflammatory cells. For each parameter except goblet cell morphology, the score ranges from 0 to 3, whereas 0 represents normal and 3 the most pathologic value. For goblet cell morphology, only the values 0 (normal) and 3 (pathologic) can be given. The mean of the pathologic value. For goblet cell morphology, only the values

### Study Design

The study was performed in a cross-sectional design. On the study day, patients arrived after they had abstained from instillation of topical lubricants for at least 24 hours. Study measurements were performed in the same order for every patient. At the beginning, a pregnancy test in women of childbearing potential was performed. Best-corrected visual acuity was assessed and patients had to fill out the OSDI questionnaire. Then, TFT, OSI, and tear osmolarity were determined. After a break of at least 10 minutes, measurement of BUT and fluorescein staining were performed. Impression cytology was taken after another break of at least 10 minutes.

### Data Analysis

Only the eye with more severe signs of DES was used for statistical analysis. Means and SD were calculated for each value. The analyses of the primary and secondary variables was performed using a linear regression analysis. Originally, a multiple regression model was planned, but due to the general lack of significant correlations, it was not employed in the final analysis. All tests were performed at the 0.05 significance level.

### Results

Fifty-two patients with DES were included in the present study (age: 46.0 ± 10.8 years, mean ± SD) of which 12 were male and 40 were female. The mean duration of DES was 5.6 ± 5.3 years. Mean BUT was 5.8 ± 2.0 seconds and OSI score was 28.9 ± 17.6, defining our study population as having generally mild to moderate DES.4,14 Table 1 shows the results obtained for all parameters assessed.

The results of the regression analysis are presented in Table 2. In general, the association between the OSI and as a subjective parameter and the measured objective variables was weak. A significant negative correlation was only found between OSI and TFT (r = -0.34, P = 0.01, Fig. 1). For all other parameters, no significant association was found, although a tendency was observed for BUT and tear osmolarity. In addition, the regression analysis revealed that the association between different signs of DES was generally weak. Tear film thickness correlated significantly positive with BUT (r = 0.35, P = 0.01, Fig. 2). In addition, a weak correlation between TFT and corneal staining score was found (r = 0.28, P = 0.04), although this finding has to be interpreted with caution, because staining was only present in seven patients.

### Discussion

Generally, the association between signs and symptoms for DES was weak in our study population, which mainly comprised of patients with a mild to moderate form of DES. The only sign that was associated with symptoms was TFT as measured using the custom-built, ultrahigh-resolution OCT. Moreover, TFT also significantly correlated with BUT, while no

<table>
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<th>Parameter</th>
<th>Mean ± SD</th>
<th>Minimum</th>
<th>Maximum</th>
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<td>BCVA, letters</td>
<td>85.0 ± 2.9</td>
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<td>OSI</td>
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<td>TFT, μm</td>
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<tr>
<td>Osmolarity, mOsm/L</td>
<td>1.2 ± 0.9</td>
<td>0.2</td>
<td>3.6</td>
</tr>
<tr>
<td>BUT, s</td>
<td>5.8 ± 2.0</td>
<td>1.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Staining score</td>
<td>0.4 ± 0.9</td>
<td>0.0</td>
<td>5.0</td>
</tr>
<tr>
<td>IC score</td>
<td>3.2 ± 2.1</td>
<td>0.2</td>
<td>7.3</td>
</tr>
</tbody>
</table>

Table 2. Results of the Linear Regression Analysis for BCVA Using ETDRS Charts, OSI, TFF, OSI, Tear Osmolarity, BUT, Corneal Fluorescein Staining (Staining Score) and Impression Cytology (IC Score)
Other correlations were found between the assessed parameters.

Our findings are in agreement with several other studies investigating the association between signs and symptoms in patients with DES or diseases accompanied with dry eye.8–10,22 The lack of correlation as observed in the present study can in principal have two reasons. On the one hand, the lack of significant association may be due to biological reasons: the measured signs have little to do with the symptoms experienced by the patient. On the other hand, our means of the measured data may suffer from errors that can either be systematic or statistic in nature.

The OSDI has been proven to be a valuable tool in the diagnosis of DES due to its high specificity and sensitivity.6,13 It correlates well with dry eye severity when determined by the physician based on several clinical assessments, however, when compared with individual assessments, the association has been found to be weak.5–13 In contrast, in a study including only healthy subjects, symptoms assessed with the OSDI significantly correlated with clinical measures usually used for the assessment of DES.23

A possible explanation for the lack of correlation between signs and symptoms in patients with DES lies within the nature of the disease. At early stages, as found in the majority of patients included in the present study, only tear film instability is present, which mainly leads to symptoms such as visual disturbances and discomfort but also to irritation of the ocular surface.4,10 At later stages, chronic inflammation occurs, which can lead to damage of subbasal corneal nerves.4,10,24 Indeed, structural alterations in corneal nerves have been found in patients with DES and the severity of the alterations also correlated to disease severity.25 This is also reflected in reduced corneal sensitivity often observed in patients with DES.26 In a study in patients with Sjögren’s syndrome, decreased corneal sensitivity was positively correlated with the severity of ocular surface disease, while symptom severity correlated negatively with disease severity.27 Therefore, it is possible that reduced corneal sensitivity at later stages of DES contributes to the inconsistency between signs and symptoms in patients with DES.

The parameter that correlated best with OSDI in our study was TFT as assessed with OCT. Average TFT values as observed in the present study in patients with TFT were considerably lower than those previously reported in healthy subjects.12 We have previously shown that in healthy subjects measurement of TFT is highly reproducible, whether this is also true in patients with DES remains unclear. It can be speculated that low TFT may be particularly found in patients with aqueous deficient DES. In meibomian gland disease (MGD)-related, evaporative dry eye, the situation might be different since tear volume may not initially be reduced.28,29

Although the present system only provides a resolution of 1.2 μm, differences between subjects much smaller than this were detected. The reason lies in the definition of resolution in OCT systems, which refers to the ability to separate two peaks within a sample structure. Theoretical considerations, however, indicate that differences as small as 50 nm in TFT can be detected.30

Another study using OCT for imaging of the tear meniscus also found that parameter to be significantly associated with the McMonnies dry-eye questionnaire.31 In contrast, in a study conducted in patients with Sjögren’s syndrome, tear meniscus did not correlate with OSDI.32 Because we did not include patients with Sjögren’s syndrome in the present study, we do not know how correlations between TFT as measured with the present OCT system and other parameters would be in that patient collective. Further studies with larger sample sizes including difference phenotypes of DES are required to better understand the potential role of TFT measurement in diagnosing patients with DES.

Objective parameters did not correlate well with each other in the present study, which may partially be related to the relatively small sample size. No association between BUT, OSI, tear osmolarity, corneal fluorescein staining, or impression cytology score were found. In the literature, findings are also inconsistent. For example, some studies found a correlation...
between BUT and tear osmolarity, while other studies did not observe this relationship.\textsuperscript{33–35} Nevertheless, most studies report no or weak correlations between the different clinical tests as it was observed in the present study.\textsuperscript{5,36} Again, one must not forget that DES is a heterogenous disease and most studies did not differentiate between phenotypes.\textsuperscript{10}

In our study, a correlation between TFT and BUT was found. This is in agreement with other studies using OCT for the assessment of tear meniscus.\textsuperscript{37,38} A thinner TFT is likely to dispose to a shorter BUT. Since the resolution of OCT is not sufficient to differentiate between the lipid layer and the aqueous layer of the tear film further studies differentiating between patients with deficient aqueous production and deficient lipid production are required to more clearly define this relation.

We also expected that reduced TFT is associated with tear osmolarity, but the correlation was only of borderline significance. Tear osmolarity is defined as the number of particles per volume of fluid and as such lower tear volume is expected to be related to increased osmolarity. Whether limited reproducibility accounts for this lack of correlation remains to be shown.

The present study has some limitations. Since the study was designed as a pilot study, we only included a relatively small sample of 52 patients with DES. Therefore, our results cannot be generalized for the whole DES population. Further, we chose to include a relatively wide spectrum of DES in our cross-sectional study, which also led to wider SD of all variables. We cannot exclude that with a higher sample size and a more defined study population, other correlations could have been found.

In conclusion, our data support the results of several other authors that in general, the association between signs and symptoms is weak in patients with DES. Tear film thickness was the only variable that correlated with an objective and a subjective parameter for the assessment of DES. Measurement of TFT with OCT therefore might become a valuable tool in the diagnosis and monitoring of DES in the future.

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