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Development of a dry eye index as a new biomarker of dry eye disease

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Abstract

Purpose: To evaluate signs and symptoms in patients diagnosed with dry eye disease (DED), divided into dry eye (DE) groups, in order to find a new biomarker that allows an accurate diagnosis, management and classification of DED.

Methods: This cross-sectional, observational study included 71 DED subjects. Subjective symptoms, visual quality and DE signs were assessed using the Ocular Surface Disease Index (OSDI), the Quality of Vision (QoV) questionnaire, best corrected distance visual acuity (VA), functional visual acuity (FVA), contrast sensitivity (CS), high- and low-order corneal aberrations (HOA and LOA, respectively), tear break-up time (TBUT), Meibomian Gland Dysfunction (MGD), Schirmer test, corneal staining, lid wiper epitheliopathy (LWE) and meibography. Participants were classified into three groups based on dryness severity using a cluster analysis, i.e., mild ($N = 17$, 55.8 ± 15.4 years), moderate ($N = 41$, 63.5 ± 10.6 years) and severe ($N = 13$, 65.0 ± 12.0). A new Dry Eye Severity Index (DESI) based on ocular surface signs has been developed and its association with symptoms, visual quality and signs was assessed. Comparisons between groups were made using Kruskal–Wallis and Chi-squared tests. Spearman correlation analysis was also performed.

Results: The DESI was based on three tests for DE signs: TBUT, Schirmer test and MGD. The DESI showed significant differences between different pairs of groups: Mild Dryness versus Moderate Dryness ($p < 0.001$), Mild Dryness versus Severe Dryness ($p < 0.001$) and Moderate Dryness versus Severe Dryness ($p < 0.001$). The DESI was significantly correlated with age (rho $= -0.30$; $p = 0.01$), OSDI score (rho $= -0.32$; $p = 0.007$), QoV score (rho $= -0.35$; $p = 0.003$), VA (rho $= -0.34$; $p = 0.003$), FVA (rho $= -0.38$; $p = 0.001$) and CS (rho $= 0.42$; $p < 0.001$) Also, significant differences between the severity groups were found for OSDI and QoV scores, VA, FVA, CS and MGD ($p < 0.05$).

Conclusions: The DESI has good performance as a biomarker for the diagnosis, classification and management of DED.

KEYWORDS
biomarker, dry eye disease, Dry Eye Severity Index, signs, symptoms

INTRODUCTION

Dry eye disease (DED) is a chronic, progressive condition of the lacrimal and meibomian glands (MGs) that results in decreased aqueous production and/or increased tear evaporation. This condition leads to hyperosmolarity and instability of the tear film surface and consequent damage to the ocular surface.[1,2]

The latest definition has been proposed by the Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS) II Definition and Classification Subcommittee. This definition states 'Dry eye (DE) is a multifactorial disease of the ocular surface, characterised by a loss of tear film homeostasis and accompanied by ocular symptoms, in which ocular surface instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play aetiological roles'.[3]

The diagnosis of DE varies depending on whether certain signs and/or symptoms are considered. The TFOS DEWS II report included a review of DED prevalence studies published worldwide between 2005 and 2015.[4] This review showed that DED prevalence ranged from 5% to 50% in studies in which the diagnosis was based on symptoms with or without signs.[4] When the diagnosis was based primarily on signs, the prevalence was as high as 75%, whereas in those studies that made the diagnosis considering both symptoms and signs, it ranged from 8.7% to 30.1%.[4]

In clinical practice, the main challenge with the diagnosis of DE is the variability between the signs and symptoms of patients.[5] DE involves different structures such as the MGs, corneal surface, tear film and a whole spectrum of cells (including Goblet, inflammatory and immune cells), making its categorisation very complex.[6,7]

The relationship between signs and symptoms when diagnosing DED is often inconsistent, indicating that certain ocular or visual markers that are effective for some patients may not apply to others.[8,9] Consequently, there is a lack of a 'gold standard' measure for identifying DED based on specific signs, symptoms or their combination. This underscores the necessity for novel diagnostic approaches integrating objective markers that align with the patients' subjective experience. While some prior studies have demonstrated a weak correlation between signs and symptoms, they often relied on a limited test battery. Conversely, studies employing a broader range of clinical tests have still failed to establish a robust association with subjective symptoms.[8–10] Thus, there is an ongoing need to develop more comprehensive diagnostic methods that better capture the complex interplay between objective signs and subjective symptoms of DED.

There are a number of specific questionnaires that subjectively evaluate DED symptoms such as the Ocular Surface Disease Index (OSDI), Dry Eye Questionnaire (DEQ)-5, McMonnies Dry Eye Questionnaire, Symptom Assessment in Dry Eye (SANDE) and the Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire.[11] They are widely employed to diagnose the condition and assess its

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Key points

- There is a lack of objective biomarkers for the diagnosis and classification of dry eye disease.
- The new Dry Eye Severity Index was significantly correlated with signs and symptoms of dry eye disease.
- The Dry Eye Severity Index could assist in the diagnosis, management and classification of dry eye disease.

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impact on the patient's quality of life.[12] One aspect directly related to the quality of life is the optical quality and visual function of the patient. Accordingly, the analysis of corneal aberrations has gained importance.[13] Previous studies have reported an increase in aberrations in eyes diagnosed with DED, and so high-order aberrations (HOA) could be a new objective tool for the assessment of DE. In addition, visual acuity (VA) and functional visual acuity (FVA) also correlated with age, with older DED patients showing worse VA and FVA.[14]

The aim of this study was to assess signs and symptoms in patients diagnosed with DED in order to find the biomarker or combination that could allow the diagnosis, characterisation and accurate relationship with subjective symptoms. A secondary aim was to compare the signs, symptoms and visual quality between participants with varying levels of DE severity.

METHODS

This cross-sectional, observational study was conducted at the TACIR Clinic, Teknon Medical Centre (Quirón Salud Group, Barcelona, Spain) in collaboration with the Laboratory of Visual Sciences and Applications (Department of Optics, University of Granada, Granada, Spain). The study was approved by the University of Granada Human Research Ethics Committee (2610/CEIH/2022). Before participating in the study, all subjects were informed of the objectives and procedures and provided written informed consent. The study was carried out in accordance with the tenets of the Declaration of Helsinki.

Participants

Seventy-one individuals diagnosed with DE were included. Participants were diagnosed with DED during the previous 12 months and had symptoms of DE for at least 3 months. DE was diagnosed if two or more abnormalities were present in the tear film or the corneal surface. The following were considered as abnormalities, and therefore as inclusion criteria: TBUT (Tear Break-Up Time) <10 s,

positive fluorescein or lissamine green staining, Schirmer test ≤10 mm after 5 min.[15] Meibomian Gland Dysfunction (MGD) was graded on a clinical scale. This scale measures the area of MG loss, with grades 0, 1, 2, 3 and 4 representing no loss, <25% loss, between 25% and 50% loss, between 51% and 75% loss and >75% glandular loss, respectively.[16] The tear meniscus study was also graded on a clinical scale. Grade 1 indicated a meniscus of variable height and regular shape with absence of debris. Grade 2 was a regular meniscus but less visible with absence of debris as well. Grade 3 indicated a diminished meniscus of irregular shape with presence of debris while grade 4 indicated an invisible meniscus.[17] Lid Wiper Epitheliopathy (LWE) of the upper eyelid was classified according to Korb's grading scale. This considers two parameters: the horizontal length of the palpebral scraper, extending from the superior point to the lateral canthus and the sagittal height (width) of the eyelid, extending from just proximal to the line of Marx to the subtarsal crease.[18,19]

Participants were excluded if they had any other ocular disease, ocular infection or active ocular allergy. They were also excluded if they had palpebral malposition, dynamic disorders, lid deformity or abnormal lid movement, had undergone ocular surgery or received general or local treatments for DED in the previous 3 months. Contact lens wearers were also excluded as this is a risk factor for MGD.[20] Other exclusion criteria were pregnancy or lactation,[21] abnormal nasolacrimal drainage, punctal plug placement within 30 days of testing or evidence of systemic disease known to affect tear production (e.g., thyroid eye disease). Additionally, subjects were excluded following the initiation of or change in dosage of any chronic systemic medication known to affect tear production, including, but not limited to, treatment with antihistamines, antidepressants, diuretics, corticosteroids or immunomodulators within 30 days of testing.

After the inclusion/exclusion criteria were verified, participants completed a battery of tests to assess the severity of DE. All of the tests listed below were performed in the order listed to avoid the more invasive tests affecting subsequent testing.[15,22] Also, all tests were performed by the same examiner to avoid the possible influence of subjective/observer variability. The results of the TBUT, Schirmer test and MGD were used to divide the participants into three levels of DE (i.e., mild, moderate, severe) as described in the statistics section below.

Subjective evaluation of symptoms of dryness and quality of vision

Two validated questionnaires were used for the assessment of subjective optical quality (Quality of Vision (QoV))[23] and DE symptomatology (OSDI).[15] The QoV questionnaire consists of 10 items including three questions related to the frequency, severity and discomfort generated by the particular symptom being assessed. Participants were asked

to score each item on a scale of 0–3 points. A total of 30 items assess symptoms such as: glare, halos, starbursts, hazy vision, blurred vision, distortion, double or multiple images, fluctuation of vision, focusing difficulties or depth perception.[23] Finally, total scores can be obtained for each subscale from 0 to 100 points, applying a Rasch scale, with higher values indicating poorer quality of vision.[24]

The OSDI questionnaire was developed to quantify the specific impact of DE on visual health-related quality of life. This 12-item questionnaire includes three subscales: ocular symptoms, vision-related daily activities and environmental triggers. For each subscale and for the questionnaire as a whole, an overall score of 0–100 was obtained, with higher values indicating greater severity of DE.[15,25]

Visual function evaluation

Visual function was assessed by several tests with subjects wearing their best subjective refractive correction where necessary. Visual acuity (VA) was measured using the Bueno-Matilla Vision Unit (MBU) (optonet.es)[26] at 6 m under photopic conditions. VA was evaluated monocularly and recorded using a logMAR scale.

FVA was also assessed in the same manner. However, FVA refers to the VA achieved after 10 s without blinking or until the patient blinked involuntarily. In this way, visual loss as a function of corneal dryness was evaluated.[27]

Contrast Sensitivity (CS) was measured monocularly with the CSV-1000 test (Vector Vision, vectorvision.com).[28] LogCS was evaluated in mesopic conditions (3 cd/m^2). The test measures spatial frequencies of 3, 6, 12 and 18 cycles per degree (cpd) and was performed at the recommended distance of 3 m.

Finally, corneal aberrometry was measured using the Pentacam AXL aberrometer-topograph (OCULUS Optikgeräte Gmbh, oculus.de/es/).[29] High- and low-order corneal aberrations (HOA and LOA) were obtained from both eyes, with Zernike polynomials up to the sixth order. The root mean square (RMS) of HOA and LOA for the anterior, posterior and total cornea were assessed with a 6 mm pupillary diameter.[29]

Ocular surface assessment and tear film function evaluation

To assess tear film stability, TBUT was measured after the installation of a drop of Colircusi Fluotest (Alcon, alcon.com). This formulation contains 2.5 mg fluorescein sodium and 4 mg oxybuprocaine hydrochloride (anaesthetic agent). While observing under cobalt blue illumination in the slit lamp biomicroscope (S360S, Shanghai MediWorks Precision Instruments, mediworks.biz) with a yellow barrier filter (Wratten number 12), the time between the last blink and the appearance of the first black spot on the corneal surface was considered as the patient's TBUT.[15] The

measurement was repeated three times on each eye and the mean value registered as the TBUT. A result <10 s was considered abnormal.[15]

As fluorescein had been instilled, signs of corneal staining were also evaluated. Four quadrants (superior, inferior, nasal and temporal) were examined for classification. The value ranged from 0 (when no quadrant was affected) to 4 (all quadrants were affected).[15]

Tear film volume was evaluated with the Schirmer test.[15] A period of 10 min was allowed after instillation of the anaesthetic to minimise the stimulatory effect of the anaesthetic sting and the volume of anaesthetic. TearFlo diagnostic strips (Madhu Instruments Pvt. Ltd, madhuinstruments.com/) were placed on the participant's temporal inferior conjunctival fornix. The test was performed with the eyes open and the subject was asked to blink for proper lacrimal stimulation. The strips were placed on each eye for 5 min, and the length of the wetted strip was checked. The strips are numbered from 1 to 35 mm so that the wetted length can be quantified. A value <10 mm after 5 min was considered as a positive for DED.[30]

The assessment of palpebral margin epitheliopathy was performed using lissamine green strips (I-DEW GREEN; Entod Research Cell UK Ltd; 1.5 mg lissamine green, entod researchcell.com). The strip was impregnated with saline solution, placed in contact with the ocular conjunctiva and examined with the slit lamp. Lid Wiper Epitheliopathy (LWE) of the upper eyelid was classified according to the Korb grading scale, as explained above.[18,19]

Finally, MGD was assessed with a portable meibographer (Me-check®, Toshbro Medicals, toshbromedicals.com) attached to the slit lamp. For the measurement, the lower eyelid was everted and a photograph was taken with the infrared camera. The resulting image was compared with an MGD severity scale included with the instrument software (Meiboscale reference scale, developed by Dr. Heiko Pult).[16] This scale follows the criteria detailed above.

Statistical analysis

All statistical procedures were performed using IBM SPSS v.28 software (ibm.com/es-es/products/spss-statistics). As the right eye was assessed first, and in order not to influence the results of the ocular surface measurements, only data from the right eye of the 71 participants were analysed.

The normality of the data distribution was evaluated using the Kolmogorov–Smirnov test. All parameters measured were not normally distributed and so non-parametric tests were used. Descriptive statistics were included with continuous variables expressed as the median and interquartile range and categorical data as number and percentages. In order to identify groups with different levels of DE severity, a two-step cluster analysis method was applied. This technique assigns participants to a cluster by minimising within-cluster variance and maximising between-cluster variance. The number of clusters was selected using the Akaike information criterion (AIC).[31] The variables that produced three groups with different severity of dryness and good cluster quality were TBUT, Schirmer test and MGD.

Signs, symptoms and visual quality comparisons between groups with different levels of dryness (mild, moderate and severe) were performed with the Kruskal–Wallis or Chi-squared tests for continuous and categorical variables, respectively. The results of multiple comparisons were adjusted with the Bonferroni correction.

A new general score of dryness on the ocular surface (Dry Eye Severity Index, DESI) was obtained. To calculate the DESI, Z-scores were first obtained for each participant using the same parameters employed in the cluster analysis (i.e., TBUT, Schirmer test and MGD). These parameters were selected because they allowed good classification or grading of the DED patients included in the study. Z-scores provide a measure of how many standard deviations an individual value lies away from the group mean. In other words, it is a statistic used to compare the result of one subject with the results of the whole group. Thus, a Z-score is computed as: $z = (x - \mu)/\sigma$ (where x is the variable value for an individual subject; μ is the mean for this variable in the group, and σ is the standard deviation of the variable for the group). Z-scores were reversed, when necessary, to achieve positive values which represented better performance than the mean. Finally, the DESI was computed as the mean z-score for each participant.[32]

In order to assess possible associations between the different parameters under investigation, Spearman correlations between age, sex, signs and symptoms of DE, visual quality and the DESI were obtained. A significance level of $p < 0.05$ was set.

RESULTS

Symptoms, visual quality and signs in dry eye patients

Descriptive data from the whole sample ($N = 71$) are shown in Table 1. The median age of the subjects was 64.0 (range 56.0–70.0) years. Twenty-six participants were male (37%) and 45 (63%) were female. A higher percentage of women with DE was found, which is in line with previous studies.[4]

The OSDI showed a median score of 33.33 (range 33.00–52.08). This represents participants with moderate DE based on their symptoms. On the other hand, the median value obtained for the QoV questionnaire was 20.00 (range 12.00–25.00), which indicates a decrease in visual quality for the items assessed in the questionnaire.

The median FVA (median = 0.20 [range 0.20–0.30]) was worse than the median VA (median = 0.02 [range −0.02–0.05]) ($Z = -10.350$; $p < 0.001$) due to the test procedure, as in subjects with DE, tear film instability will affect VA as a function of the time without blinking. As expected, the

TABLE 1 Descriptive statistics of the sample (*N* = 71).

Variable	Median (IQR)/*N*	Range/%
Age (years)	64.00 (56.00 to 70.00)	32 to 85
Sex		
Male	26	36.60
Female	45	63.40
OSDI total score	33.33 (33.00 to 52.08)	4.16 to 85.00
OSDI (classification)		
Normal	6	8.50
Mild	12	16.90
Moderate	15	21.10
Severe	38	53.50
QoV score	20.00 (12.00 to 25.00)	1.00 to 60.00
VA (logMAR)	0.02 (−0.02 to 0.05)	−0.12 to 0.60
FVA (logMAR)	0.20 (0.20 to 0.30)	0.10 to 1.00
Contrast sensitivity (LogCS)		
3 cpd	1.63 (1.49 to 1.78)	1.00 to 1.93
6 cpd	1.84 (1.84 to 1.99)	1.38 to 2.14
12 cpd	1.54 (1.54 to 1.69)	1.08 to 1.99
18 cpd	1.10 (1.10 to 1.15)	0.64 to 1.55
Average	1.57 (1.46 to 1.64)	1.02 to 1.79
RMS total (cornea)	1.43 (1.17 to 1.92)	0.78 to 4.82
RMS total (ant.cornea)	1.57 (1.34 to 1.90)	0.92 to 4.51
RMS total (post. cornea)	0.73 (0.62 to 0.90)	0.39 to 2.11
RMS LOA (cornea)	1.28 (1.03 to 1.83)	0.73 to 4.17
RMS LOA (ant.cornea)	1.55 (1.24 to 1.82)	0.63 to 3.96
RMS LOA (post. cornea)	0.71 (0.59 to 0.71)	0.36 to 2.03
RMS HOA (cornea)	0.50 (0.39 to 0.63)	0.25 to 2.42
RMS HOA (ant.cornea)	0.45 (0.38 to 0.58)	0.25 to 2.16
RMS HOA (post. cornea)	0.18 (0.16 to 0.20)	0.11 to 0.57
TBUT (s)	6.00 (5.00 to 7.00)	2.00 to 13.00
Schirmer test (mm/5 min)	10.00 (7.00 to 14.00)	2.00 to 35.00
Corneal staining		
0	53	74.60
1	15	21.10
2	3	4.20
MGD		
1	18	25.40
2	40	56.30
3	13	18.30

Note: Continuous variables are included as mean ± SD and categorical data are shown as *N* and percentages (%).

Abbreviations: ant, anterior; cpd, cycles per degree; CS, contrast sensitivity; FVA, functional visual acuity; HOA, high-order aberrations; IQR: interquartile range; LOA, low-order aberrations; MGD, meibomian gland dysfunction; OSDI, ocular surface disease index; post, posterior; QoV, quality of vision; RMS, root mean square; TBUT, tear brake-up time; VA, visual acuity.

median TBUT value was <10 s (median = 6.00 s [range 5.00–7.00 s]), based on the inclusion criteria for DE. However, the results of the Schirmer test were more variable, with a median (range) of 10.00 (7.00–14.00) mm in 5 min. Additionally, some subjects demonstrated values above the limit expected for DE.

Most participants had no corneal staining or only slight staining in just one quadrant. With regard to MGD, most participants were graded as 2, and none had the most severe grade of 4.

Symptoms, visual quality and signs in groups with varying severity of dry eye

With the aim of classifying subjects based on the DE signs at the ocular surface, a cluster analysis was employed. The variables that provided good cluster quality were the Schirmer test, MGD and TBUT. A two-step cluster analysis identified three groups based on these variables (i.e., mild, moderate and severe dryness). The silhouette value of cohesion and separation indicated good cluster quality (see Figure 1).

Table 2 shows results categorising the entire sample into mild (MiD), moderate (MD) and severe dryness (SD) based on the ocular surface signs. While greater dryness was associated with older age, no statistical differences were found ($p = 0.05$). In terms of gender distribution, the MiD group had a higher percentage of males (59%), whereas the MD and SD groups had more females (76% and 54%, respectively). The Chi-squared test showed significant differences in gender distribution between the groups ($p = 0.03$).

Pairwise comparisons with the Kruskal–Wallis test showed significant differences in some of the parameters being assessed. Firstly, the questionnaire symptom scores showed significant differences between the groups in terms of DE severity. The SD group showed significantly higher scores in both subjective quality of vision (QoV) and dryness symptoms as assessed by the OSDI than the MiD ($p = 0.003$ and $p = 0.01$, respectively) and MD ($p = 0.006$ and $p = 0.02$, respectively) groups.

FIGURE 1 Silhouette measure of cluster quality for grouping subjects with different levels of dryness at the ocular surface.

TABLE 2 Comparison between the dryness groups (significant differences are shown in bold).

Variable	Mild dryness (MiD) N = 17 Median (IQR)/N (%)	Moderate dryness (MD) N = 41 Median (IQR)/N (%)	Severe dryness (SD) N = 13 Median (IQR)/N (%)	Statistic (H/χ^2)	p-Value	Multiple comparisons
	Group					
Age (years)	57.00 (40.00–66.50)	65.00 (58.00–71.50)	66.00 (60.50–72.50)	5.99	0.05	
Sex						
Male	10 (58.8%)	10 (24.4%)	6 (46.2%)	6.76	**0.03**	
Female	7 (41.2%)	31 (75.6%)	7 (53.8%)			
OSDI total score	25.00 (14.58–51.04)	31.25 (21.35–48.00)	54.16 (41.18–66.66)	9.53	**0.009**	MiD–SD (**p = 0.01**)
						MD–SD (**p = 0.02**)
QoV score	15.00 (6.00–24.00)	18.00 (12.50–24.00)	25.00 (22.50–29.50)	12.23	**0.002**	MiD–SD (**p = 0.003**)
						MD–SD (**p = 0.006**)
VA (logMAR)	−0.04 (−0.08–0.00)	0.02 (0.00–0.06)	0.02 (0.00–0.07)	9.63	**0.008**	MiD–MD (**p = 0.009**)
						MiD–SD (**p = 0.049**)
FVA (logMAR)	0.20 (0.10–0.20)	0.30 (0.20–0.30)	0.30 (0.20–0.40)	9.69	**0.008**	MiD–MD (**p = 0.01**)
						MiD–SD (**p = 0.04**)
Contrast sensitivity (LogCS)						
3 cpd	1.63 (1.63–1.78)	1.63 (1.49–1.63)	1.49 (1.49–1.78)	5.31	0.07	
6 cpd	1.99 (1.84–1.99)	1.84 (1.84–1.99)	1.84 (1.70–1.92)	8.47	**0.01**	MiD–SD (**p = 0.02**)
12 cpd	1.69 (1.69–1.84)	1.54 (1.54–1.69)	1.54 (1.40–1.69)	12.22	**0.004**	MiD–MD (**p = 0.01**)
						MiD–SD (**p = 0.008**)
18 cpd	1.25 (1.10–1.25)	1.10 (1.10–1.25)	1.25 (0.96–1.25)	2.45	0.29	
Average	1.68 (1.59–1.70)	1.57 (1.46–1.62)	1.53 (1.40–1.61)	9.94	**0.007**	MiD–MD (**p = 0.02**)
						MiD–SD (**p = 0.02**)
RMS total (cornea) (µm)	1.48 (1.24–1.73)	1.38 (1.15–1.99)	1.31 (1.12–2.12)	0.102	0.95	
RMS total (ant.cornea) (µm)	1.67 (1.30–1.94)	1.55 (1.34–1.87)	1.56 (1.15–2.05)	0.150	0.93	
RMS total (post. cornea) (µm)	0.75 (0.60–0.88)	0.73 (0.63–0.92)	0.70 (0.61–0.88)	0.066	0.97	
RMS LOA (cornea) (µm)	1.39 (1.06–1.67)	1.26 (1.02–1.91)	1.28 (1.01–1.97)	0.06	0.97	
RMS LOA (ant.cornea) (µm)	1.63 (1.13–1.85)	1.48 (1.26 –1.82)	1.52 (1.06–1.91)	0.17	0.92	
RMS LOA (post. cornea) (µm)	0.71 (0.57–0.86)	0.71 (0.60–0.90)	0.67 (0.59–0.86)	0.10	0.95	
RMS HOA (cornea)	0.48 (0.37–0.67)	0.49 (0.39–0.63)	0.53 (0.39–0.76)	0.78	0.68	
RMS HOA (ant.cornea)	0.51 (0.40–0.64)	0.43 (0.37–0.58)	0.51 (0.36–0.68)	1.83	0.40	
RMS HOA (post. cornea)	0.18 (0.16–0.22)	0.18 (0.16–0.20)	0.17 (0.16–0.21)	0.17	0.92	
TBUT (s)	9.00 (7.50–11.50)	6.00 (5.00–7.00)	4.00 (3.00–5.00)	32.32	**<0.001**	MiD–MD (**p < 0.001**)
						MiD–SD (**p < 0.001**)
						MD–SD (**p < 0.001**)
Schirmer test (mm/5 min)	12.00 (10.00–24.00)	10.00 (7.00–13.00)	10.00 (8.00–11.00)	5.16	0.08	
Corneal staining						
0	14 (82.3%)	31 (75.6%)	8 (61.5%)	7.48	0.11	
1	1 (5.9%)	10 (2.4%)	4 (30.8%)			
2	2 (11.8%)	0 (0%)	1 (7.7%)			

TABLE 2 (Continued)

	Group					
	Mild dryness (MiD)	**Moderate dryness (MD)**	**Severe dryness (SD)**			
	$N = 17$	$N = 41$	$N = 13$	**Statistic**		**Multiple**
Variable	**Median (IQR)/N (%)**	**Median (IQR)/N (%)**	**Median (IQR)/N (%)**	(H/χ^2)	**p-Value**	**comparisons**
MGD						
1	17 (100%)	1 (2.4%)	0 (0%)	136.42	**<0.001**	
2	0 (0%)	40 (97.6%)	0 (0%)			
3	0 (0%)	0 (0%)	13 (100%)			
LWE						
0	16 (94.12%)	31 (75.61%)	9 (69.24%)	7.43	0.12	
1	1 (5.88%)	9 (21.95%)	2 (15.38%)			
2	0 (0%)	1 (2.44%)	2 (15.38%)			

Abbreviations: ant, anterior; cpd, cycles per degree; CS, contrast sensitivity; DESI, Dry Eye Severity Index; FVA, functional visual acuity; IQR, interquartile range; LOA, low-order aberrations; HOA, high-order aberrations; MGD, Meibomian Gland Dysfunction; LWE, Lid Wiper Epitheliopathy; OSDI, ocular surface disease index; QoV, quality of vision; post, posterior; RMS, root mean square; TBUT, tear break-up time; VA, visual acuity.
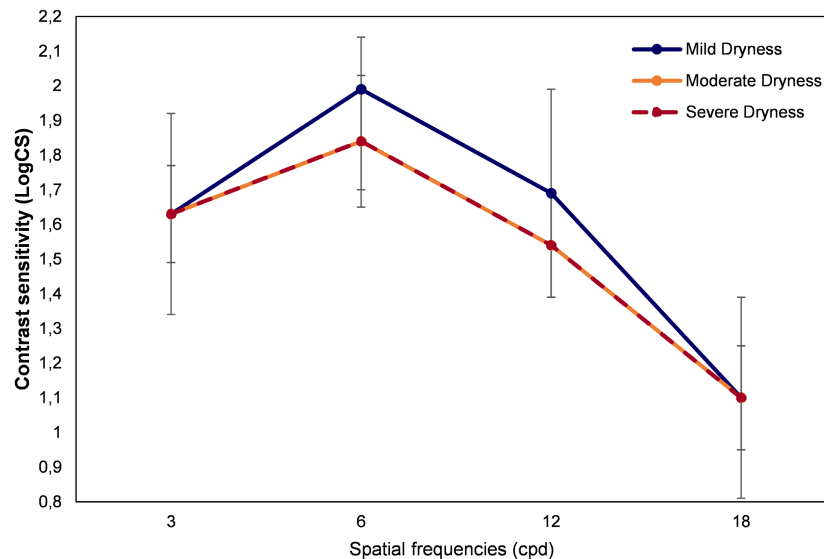

FIGURE 2 Contrast Sensitivity (CS) Function (LogCS) of the different levels of dryness. The error bars represent the interquartile range (IQR). cpd, cycles per degree.

Visual function and optical quality parameters showed significant differences between the dryness severity groups. VA was significantly better in the MiD group than the MD ($p = 0.009$) and the SD ($p = 0.049$) group. Similar findings were observed for functional visual acuity, which demonstrated an increase of 45% for both the MD and SD groups ($p = 0.01$ and $p = 0.04$, respectively) with respect to the MiD group.

There were significant differences between the groups for contrast sensitivity at the medium spatial frequencies assessed (6–18 cpd) (Table 2 and Figure 2). CS of the MiD group was significantly higher than the MD group at 12 cpd ($p = 0.01$) and significantly higher than the SD group at 6 and 12 cpd ($p = 0.02$ and $p = 0.02$). Average CS function was also significantly reduced in the MD ($p = 0.02$) and SD ($p = 0.02$) groups with respect to the MiD group. Finally, LOA

and HOA did not show significant differences between the severity groups for the anterior, posterior and total cornea.

Comparison of parameters that assessed DE signs at the ocular surface also indicated significant differences between groups (Table 2). This result was expected, particularly for those variables used in the cluster to classify the sample into severity groups. Thus, tear film stability as assessed by the TBUT was not only significantly lower in the MD and SD groups with respect to the MiD group ($p < 0.001$) but also in the SD compared with the MD group ($p < 0.001$). Although median tear volume as measured with the Schirmer test decreased for the MD and SD groups, these differences were not statistically significant ($p = 0.08$). Chi-squared tests also indicated significant differences in the distribution of scores for the MGD ($p < 0.001$).

In order to obtain a general measure of dryness from the ocular surface measures, the DESI was calculated. These values are shown in Figure 3 for the three groups, with more negative values indicating greater dryness. The Kruskal–Wallis test showed significant differences between pairs of groups: MiD versus MD ($p < 0.001$), MiD versus SD ($p < 0.001$) and MD versus SD ($p < 0.001$).

Association between symptoms, visual quality and the DESI

Spearman's correlations between age, sex, DE symptoms, the optical parameters and signs are shown in Table 3. Older participants had a higher score on the QoV test and therefore they perceived their quality of vision to be poorer ($p = 0.047$). The OSDI findings showed a significant correlation with the degree of MGD ($p = 0.002$), indicating a higher incidence of DE symptoms in subjects with a greater degree of MGD. The QoV test showed a significant correlation with both MGD ($p = 0.001$) and the OSDI questionnaire score ($p < 0.001$). This means that greater degrees of MGD were associated with a higher incidence of visual symptoms (QoV). On the other hand, those subjects with more symptoms (based on their OSDI) also reported more visual symptoms in the QoV questionnaire ($p < 0.001$).

The DESI showed a significant correlation with age ($p = 0.01$), VA ($p = 0.003$), FVA ($p = 0.001$), CS ($p < 0.001$), OSDI score ($p = 0.007$) and QoV test score ($p = 0.003$). Older patients had worse DESI values, that is, greater DE severity. The higher the DESI, the worse the VA and FVA results. Likewise, those patients with higher DESI also showed poorer contrast sensitivity, suggesting that this index is a good indicator of visual quality. Lastly, results showed that the higher the DESI, the worse the results in the subjective DE symptoms score (OSDI) and the visual quality symptoms score (QoV).

DISCUSSION

The diagnosis of DED is inherently complex, mainly due to the lack of consistency between the patient's clinical signs and symptoms.[5] Previous studies have shown that individual's symptomatology is not always related to clinical signs, even in samples of participants diagnosed with DE and compared with control or healthy groups for clinical signs.[9,33]

This study investigated which markers might be the best indicators of DED. The relationship between symptoms, visual quality and signs in individuals diagnosed with DED was studied. For this purpose, both objective tests and subjective questionnaires on DE and visual quality were used. The study also incorporated the objective evaluation of ocular aberrations in order to understand better the visual quality of DED subjects.

Cluster analysis identified three levels of DE severity based on MGD, TBUT and the Schirmer test. These parameters were applied to determine a DESI which was significantly correlated with symptoms (OSDI and QoV), and measures of visual quality (FVA, CS and total corneal RMS). The new biomarker was shown to be predictive and reliable in identifying the severity of DE pathology, as higher index values were found in the SD group with respect to the MD or MiD groups. Further, the DESI based MiD group had better visual quality than subjects in the MD or SD groups. These differences indicate that the new DESI can be a useful tool in the diagnosis of DED.

The finding that the DESI based MiD group had better visual quality than participants in the MD or SD groups is consistent with previous studies where poorer visual quality was observed in individuals diagnosed with DE disease, compared with control groups.[34] Similarly, participants in this study also generally showed worse CS and VA than those of similar age without DED.[35]
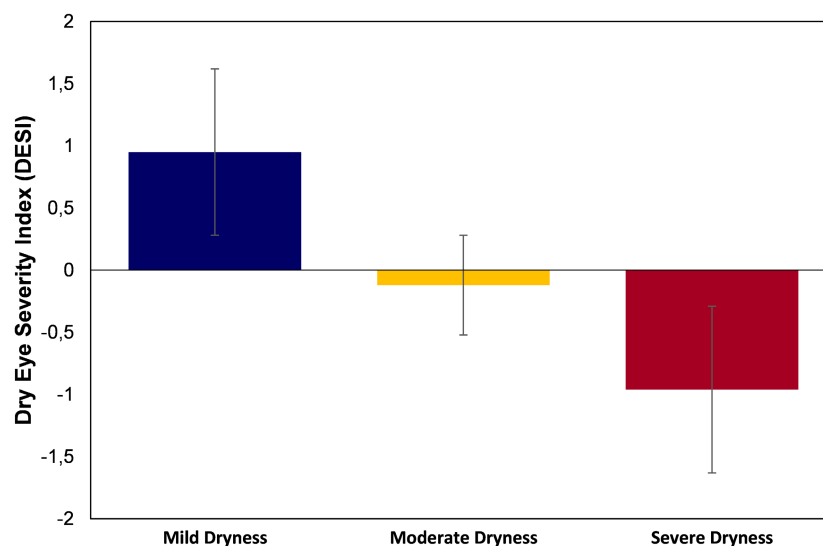

FIGURE 3 Dry Eye Severity Index (DESI) for the three groups of dry eye participants. The error bars represent the interquartile range (IQR). More negative DESI values indicate greater dryness.

TABLE 3 Spearman correlations between age, sex, dry eye signs, symptoms, optical quality parameters and the Dry Eye Severity Index.

	1	2	3	4	5	6	7	8	9	10	11	12	13
(1) Age (years)	—												
(2) Gender	0.06 0.65	—											
(3) OSDI total score	-0.12 0.16	0.29 **0.02**	—										
(4) QoV score	-0.17 0.05	0.22 0.06	0.74 **<0.001**	—									
(5) VA (logMAR)	0.54 **<0.001**	0.18 0.14	-0.08 0.50	-0.01 0.92	—								
(6) FVA (logMAR)	0.24 0.05	0.13 0.28	0.09 0.48	0.07 0.56	0.56 **<0.001**	—							
(7) Mean contrast sensitivity (LogCS)	-0.34 **0.003**	-0.24 0.05	-0.11 0.38	-0.10 0.41	-0.67 **<0.001**	-0.63 **<0.001**	—						
(8) RMS total (cornea)	0.22 0.07	-0.03 0.79	-0.01 0.93	-0.03 0.80	0.08 0.49	0.18 0.14	-0.11 0.35	—					
(9) RMS LOA (cornea)	0.16 0.17	-0.02 0.85	-0.01 0.91	-0.04 0.77	0.05 0.68	0.12 0.31	-0.08 0.49	0.98 **<0.001**	—				
(10) RMS HOA (cornea)	0.51 **<0.001**	-0.09 0.48	-0.09 0.48	-0.11 0.36	0.32 **0.007**	0.33 **0.005**	-0.13 0.29	0.58 **<0.001**	0.47 **<0.001**	—			
(11) Corneal staining	-0.06 0.60	0.09 0.47	-0.05 0.68	0.03 0.81	0.07 0.57	-0.02 0.89	0.02 0.85	-0.13 0.26	-0.15 0.21	-0.06 0.61	—		
(12) LWE	0.23 0.05	0.02 0.87	0.07 0.56	0.10 0.41	0.20 0.10	0.01 0.93	-0.06 0.64	0.11 0.37	0.12 0.32	0.14 0.26	-0.07 0.58	—	
(13) DESI	-0.30 **0.01**	-0.19 0.11	-0.32 **0.007**	-0.35 **0.003**	-0.34 **0.003**	-0.38 **0.001**	0.42 **<0.001**	0.01 0.93	0.03 0.84	-0.10 0.41	-0.10 0.39	-0.07 0.56	0.56

Spearman's rho (top) and corresponding *p*-value (bottom) are shown for each correlation. Statistically significant *p*-values are shown in bold font. Abbreviations: CS, contrast sensitivity; DESI, Dry Eye Severity Index; FVA, functional visual acuity; HOA, high-order aberrations; LOA, low-order aberrations; LWE, Lid Wiper Epitheliopathy; MGD, Meibomian Gland Dysfunction; OSDI, ocular surface disease index; QoV, quality of vision; RMS, root mean square; TBUT, tear brake-up time; VA, visual acuity.

In terms of specific tests to measure and observe signs of DE (i.e., TBUT, Schirmer test, MGD, corneal staining and LWE), lower TBUT values were found in the group with more severe DE (SD group). This suggests that TBUT could be used as a clinical sign, not only to diagnose the condition, to indicate the severity of the DE. Several studies have indicated the importance of this clinical test in the assessment of DED, obtaining lower values in subjects with DE.[28,36]

The present investigation did not find a significant correlation between TBUT and an increase in HOA ($p = 0.63$). This is in contrast to a previous study which did report a significant increase in HOA in subjects with reduced TBUT.[38] One reason for this discrepancy could be the variability in the results obtained during the measurement of ocular aberrations, as well as other factors such as tearing, blinking or even the repeatability of the measuring device.[29,37]

The variability of DE resulted in differences in degrees of subjective symptoms. The OSDI scores were worse in the SD and MD group. This result shows the usefulness of this particular questionnaire to identify the severity of DED, in agreement with other studies.[12] The results from QoV survey were similar to those obtained with the OSDI, suggesting poorer outcomes for groups with more severe dryness. A significant correlation was observed between the OSDI and QoV findings, indicating that visual quality was worse with more severe DED. This is in line with previous studies that evaluated changes in HOA and tear film instability, and showed that poorer QoV scores were associated with higher degrees of ocular dryness.[13,23]

The DESI findings were significantly correlated with subjective questionnaires for visual quality and DE (i.e., QoV and OSDI, respectively). The DESI score was developed with tests aimed at evaluating signs of DE, so this correlation with the questionnaires, which have previously been found to be reliable and predictive in different studies, is to be expected.[12,23,39] The finding that the DESI was significantly correlated with VA, FVA and CS is also in line with studies showing that the visual quality declines in individuals with DE.[34,40–42]

These results suggest the DESI is a useful biomarker that could assist in the diagnosis and classification of DED. Although the index was obtained from ocular surface parameters (TBUT, Schirmer test and MGD), correlations with visual parameters and subjective symptomatology questionnaires have been established. This is important if the DESI is to be considered in the management of DED.

Ocular aberrations, specifically HOA RMS, only showed a strong correlation with VA and FVA. The evaluation of aberrations as a function of Zernike polynomials was not conducted; rather, the RMS of the total high- and low-order aberrations was determined. Previous studies, in which HOA segmented by the different Zernike polynomials were evaluated, have shown an increase in HOA in different polynomials (i.e., total, spherical and coma).[13,43]

This study has a number of limitations that should be considered when interpreting the results. Firstly, a single examiner performed all the testing, so they could have been influenced by knowing previous results. Secondly, the absence of a control group precludes a comparison with healthy individuals, which would enhance the validation of the DESI index. Future studies should include a control group to validate this new metric further. Thirdly, the results were based on a limited sample, with groups comprising different numbers of participants and gender distributions. Future studies should include larger samples to obtain more homogeneous groups in terms of size and gender. Finally, non-invasive tear breakup time (NIBUT) was not measured here. While TBUT and NIBUT are both valid parameters for assessing DED patients according to the TFOS DEWS II, the use of NIBUT is recommended. The present investigation used TBUT to take advantage of the fact that the eye was anaesthetised in preparation for the Schirmer test, although this could also be considered a limitation.

Future studies should investigate how the DESI changes following DE treatments such as MGs expression or intense pulsed light (IPL). In addition, it should also be applied to other populations. This will help develop a normative database and threshold levels for the diagnosis and classification of DED.

CONCLUSIONS

The diagnosis and management of DE has become increasingly common around the world; however, the evaluation is complex due to its aetiology and the marked variability between signs and symptoms. The use of new tools is necessary for the correct management of this condition. This study described the new DESI which showed a significant correlation with signs and symptoms of DE. It will be useful to determine the severity and to compare signs, symptoms and visual quality amongst individuals with varying levels of DE. While these results are promising, the index does require further validation.

AUTHOR CONTRIBUTIONS

César Gala-Núñez: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); writing – original draft (equal); writing – review and editing (equal). **Sonia Ortiz-Peregrina:** Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); project administration (equal); supervision (equal); writing – review and editing (equal). **Diego Castanera-Gratacós:** Conceptualization (equal); investigation (equal); methodology (equal); writing – review and editing (equal). **Rosario G. Anera:** Conceptualization (equal); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); supervision (equal); writing – review and editing (equal).

CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest and have no proprietary interest in any of the materials mentioned in this article.

DATA AVAILABILITY STATEMENT

The data sets generated during the current study are available from the corresponding author on reasonable request.

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