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ABSTRACT

Purpose: Vital staining is one of the most widely test used to evaluate the corneal damage. The aim of this study was to assess the relationship of the corneal damage with tear meniscus height (TMH) and dry eye symptomatology. **Material and methods:** 530 subjects were recruited among patients of the Optometry Clinic (USC). Previously, all of them completed an OSDI questionnaire. Two videos of the ocular surface were recorded from each patient by a digital camera attached to a slit-lamp. Firstly, a video of central tear meniscus under 40x with the Tearscope device illumination was recorded. From those videos, a masked observer extracted one image and TMH was measured by using the ImageJ software. Secondly, after fluorescein instillation, the corneal surface was recorded by another experienced masked observer, who assigned a category to the corneal damaged based on the Oxford Scheme. The evaluation was stratified by corneal zones based on the CCLRU grading scales (central, superior, inferior, nasal and temporal). **Results:** When the sample was grouped by the corneal staining Oxford Grade, there was found a statistical difference between groups in OSDI and TMH value (ANOVA: both $p \leq 0.006$). There was found a difference in OSDI value when corneal damage was in nasal or inferior areas (t-test; both $p \leq 0.015$), and a difference in TMH value arises when damage was in the central, nasal or inferior areas (t-test; all $p \leq 0.013$). **Conclusions:** There is a relationship between corneal damage grade and corneal zones with dry eye symptomatology and tear film volume.

Keywords: Corneal staining, Dry Eye symptomatic assessment, Tear Meniscus Height, Oxford Scheme, CCLRU grading scales, Tearscope

1. INTRODUCTION

According to the Tear Film and Ocular Surface Society Dry Eye Workshop, Dry eye disease (DED) is a common problem that results in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease [1, 2]. The characteristic features of DED are changes in the composition of the tear film and inflammation of the ocular surface. All those events induce inflammatory events that negatively affect ocular surface cells leading to symptoms such as eye irritation and blurred vision with impacts on quality of life [2, 3].

Corneal or bulbar staining are one of the most widely test used in the ocular surface damage assessment during dry eye diagnosis, despite the fact that the interpretations and significations are still not clear [4-10]. On the other hand, symtomps are commonly aproched with specific dry eye questionnaries such as such the Ocular Surface Disease Index [OSDI] [11, 12]. Tear film volume is one of the key components of tear dynamics [3, 13, 14]; where tear meniscus evaluation offers a non-invasive indication of the total volume of the tear film, since it is directly related with the total tear film volume [13-16]. The aim of this study was to assess the relationship of the corneal damage with TMH and dry eye symptomatology.

2. MATERIAL AND METHODS

2.1 Sample

This study was conducted in a group of 530 subjects (201 men, 329 women) of mean age 37.9 ± 16.66 years (18 to 76 years). Patients were recruited among subjects visiting the Optometry Clinic of the Optometry Faculty (USC, Spain) for an eye examination. Subjects were excluded if they had a history of conjunctival, scleral, or corneal disease, prior eye surgery, glaucoma, diabetes mellitus or a thyroid disorder. No participant was under any type of medication or used

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artificial tears at the time of the testing session. The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of the USC. Only the right eye was examined because of induced excess tearing in the second eye and to avoid overstating the precision of statistical estimates [17]. Throughout the study, laboratory conditions of temperature, light, and humidity were kept constant (20-23°C, relative humidity 50-60%).

2.2 Ocular Surface Disease Index (OSDI)

Prior to the tear film parameter recording, The OSDI (Allergan Inc., Irvine, California) [12] was performed. It is a 12-item self-administered questionnaire designed to provide rapid assessment of the range of ocular surface symptoms related to chronic DED, severity and their effects on the patient's ability to function. Total OSDI scores were calculated according to published guidelines [OSDI score = (Sum of question scores x 25)/ number of questions answered], with a final score ranging from 0 to 100 [11, 12].

2.3 Tear Meniscus evaluation

Subjects were positioned at the slit-lamp and instructed to look at a target located to maintain primary eye gaze and lower tear meniscus was observed by a Topcon SL-D4 biomicroscope with a naturally blink. Meniscus videos were recorded by a Topcon DV-3 digital camera attached to the slit-lamp and stored by a connected computer via Topcon IMAGEnet i-base. Lower tear meniscus was videotaped with Tearscope™ Plus (Keeler, Windsor, UK) [18, 19] fixed to the slit-lamp to keep the distance between the chinrest and the device constant during the imaging capture. During all the study, the illumination was provided by the Tearscope (the slit-lamp was switched off). This device offers two sets of illumination; in all the measurements, the brightest one was used.

Tear meniscus images extracted from recordings by a second masked observe, and TMH measured by computer-assistance image analysis using ImageJ software v1.49b (National Institutes of Health, Bethesda, MD; http://imagej.nih.gov/ij/) [20-22]. In all cases the meniscus image selection always followed the same criteria: after the last blinking, the image was captured when the meniscus was stable with minimal changes and completely expanded. TMH was marked with the *straight* tool, which allows the user to set a line with a free size and position. The line was picked in the middle of the illuminated area and perpendicular to the eyelid margin, from the lowest limit to the highest one depending on the meniscus parameter. Then, the length was calculated using the command *Analyse* > *Measure* and the software gives the parameter length on pixels. The correspondence between real millimetres and pixels counted with ImageJ software with a pre-study analysis (1 real millimetre = 300 pixels counted by ImageJ).

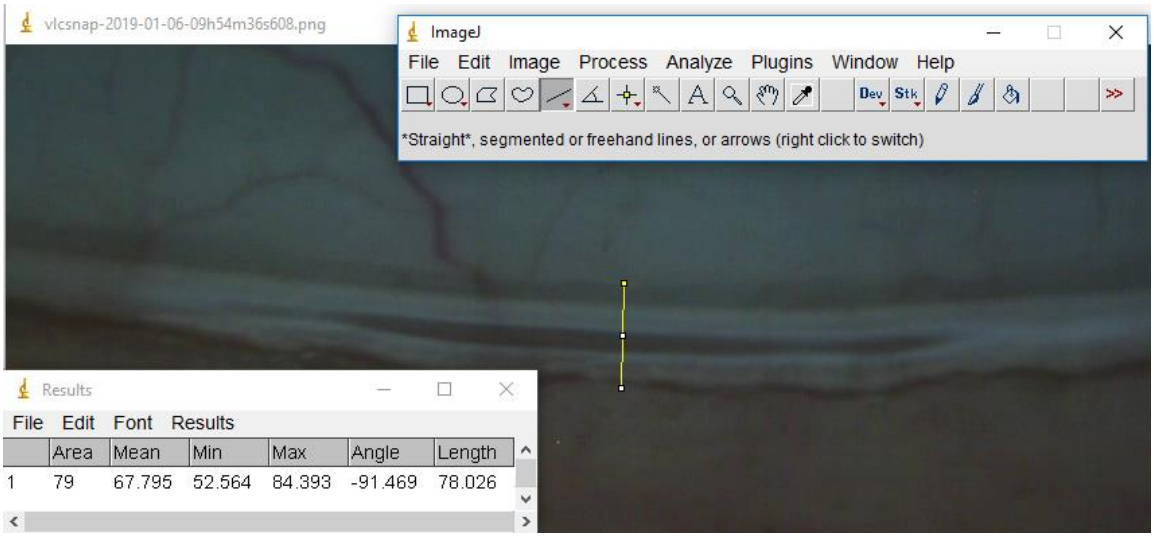

Figure 1. Example of a TMH under Tearscope device illumination measured by ImageJ software

2.4 Corneal staining evaluation

Ten minutes later to tear meniscus recording, 2 µl volume of non-preserved 2% sodium fluorescein was instilled into the conjunctival sac with a micro-pipette; the subject was instructed to blink several times naturally, without squeezing, to evenly distribute it over the cornea [6, 23, 24]. Within 30 seconds of instillation, the eye was observed by the slit-lamp

biomicroscope, using a cobalt blue filter and a Wratten 12 yellow filter to enhance tear film visibility [23, 24]. When the situation required it, the upper eyelid is lifted slightly to evaluate the whole corneal surface [6].

A masked observer evaluates de recordings and classifies the corneal staining following the Oxford Classification, a 0 to 4 grade from no presence to pathological damage (Figure 2A) [6, 24]. In addition, following the CCLRU, the location of the staining was also indicated (Figure 2B) [4-9, 24].

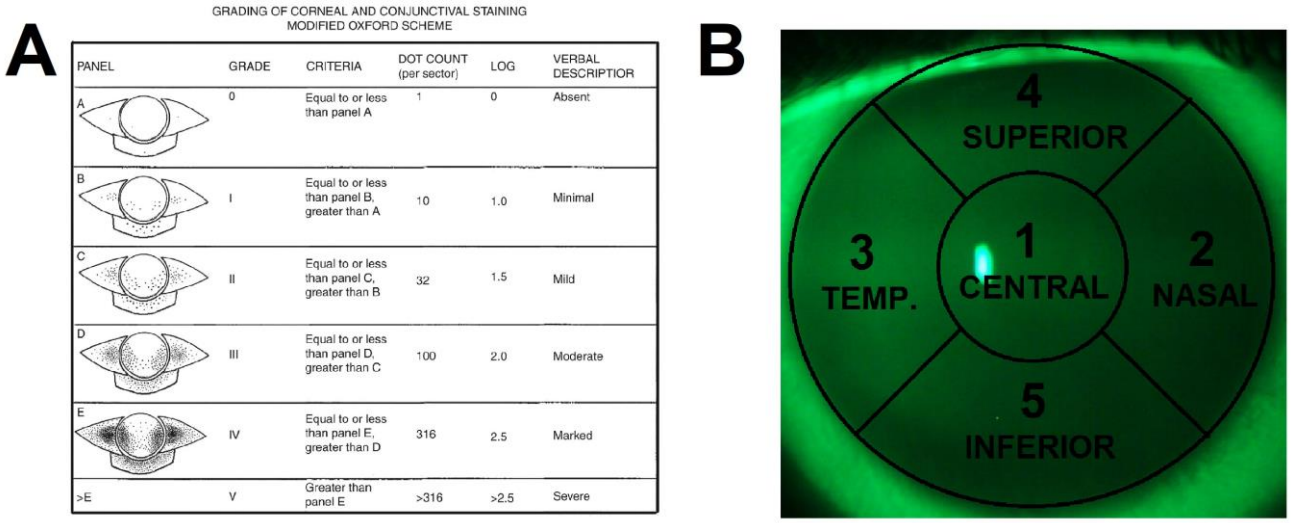

Figure 2. Corneal staining scales used to categorise the corneal damage [24]. A) Oxford Classification. B) Corneal zones based on the CCLRU grading scales.

2.5 Statistical analysis

SPSS statistical software v.19.0 for Windows (SPSS Inc., Chicago, IL) was used for data analysis. For all statistical tests, significance was set at a $p \leq 0.05$. First, a one-way analysis of variance (ANOVA) was used to determine the differences in OSDI scores as well as TMH values between Oxford Classification categories [25]. Second, an impaired t-test was used to assess differences of OSDI and TMH values between subjects split into two groups by the presence or not of staining on each of the areas established by the CCLRU.

3. RESULTS

Table 1 shows the descriptive statistics of the parameters analysed in the study. Regarding corneal staining Oxford Grade, from the 530 participants, 346 showed no staining or Grade 0 (65.2%), 106 showed slight staining or Grade 1 (20.0%), 57 showed moderate staining or Grade 2 (10.8%), 16 showed a marked staining or Grade 3 (3.0%), and 5 showed a pathological staining or Grade 4 (1.0%). Regarding the area where the damage was located, from the 530 participants, 52 showed corneal staining in the central area or Area 1 (9.8%), 93 showed corneal staining in the nasal area or Area 2 (17.5%), 66 showed corneal staining in the temporal area or Area 3 (12.5%), 40 showed corneal staining in the superior area or Area 4 (7.5%), and 174 showed corneal staining in the superior area or Area 5 (32.8%).

Table 1. Descriptive statistics of the parameters analysed in the study. Oxford Grade and OSDI score are no dimensional parameter. TMH values are provided in mm. n = 530 subjects. OSDI = Ocular Surface Disease Index. TMH = Tear Meniscus Height. SD = Standard Deviation.

	Mean	SD	Minimum	Maximum
Oxford Grade	0.54	0.87	0.00	4.00
OSDI	20.89	18.75	0.00	72.92
TMH	0.166	0.060	0.03	0.52

3.1 Analysis of the relationship between corneal staining and symptomatic assessment

There was found a statistical difference in the OSDI score parameter between groups when the sample was grouped by Oxford Grade (ANOVA: p = 0.006; Table 2). The relationship between the symptomatology studied by OSDI and the location of the staining was analysed area by area. In each analysis, the sample was split by the presence or not of corneal staining in the studied area, and the difference in the OSDI score was assessed. There was found a statistical difference in OSDI score value between participants split by the presence or not of staining only when corneal damage was located in the nasal (impaired t-test; p = 0.008) or inferior areas (impaired t-test; p = 0.015) (Table 3).

Table 2. Descriptive statistics and differences (ANOVA) in the OSDI score between participants grouped by Oxford Grade. Oxford Grade and OSDI score are no-dimensional parameter. OSDI = Ocular Surface Disease Index. SD = Standard Deviation.

		OSDI		
Oxford Grade	**n**	**Mean**	**SD**	
0	346	19,29	14,94	0.006
1	106	23.44	16.06	
2	57	22.59	15.77	
3	16	30.73	16.33	
4	5	26.14	9.75	

Table 3. Differences (paired t-test) and 95% limits of agreement between subjects grouped by the presence or not of staining in each corneal area. Oxford Grade and OSDI score are no-dimensional parameter. OSDI = Ocular Surface Disease Index. SD = Standard Deviation. 95% LoAs = 95% Limits of Agreement.

			OSDI score				
Area	**Presence of staining**	**n**	**Mean ± SD**	**Mean Difference ± SD**	**p**	**95% LoA**	
						Lower	**Upper**
Area 1 (Central)	No presence	478	20.73 ± 15.59	- 1.52 ± 2.07	0.467	-5.58	2.54
	Presence	52	22.26 ± 14.05				
Area 2 (Nasal)	No presence	437	20.07 ± 14.90	- 4.67 ± 1.75	0.008	-8.10	-1.24
	Presence	93	24.74 ± 17.30				
Area 3 (Temporal)	No presence	464	20.72 ± 15.65	- 1.34 ± 1.85	0.472	-4.97	2.29
	Presence	66	24.74 ± 17.30				
Area 4 (Superior)	No presence	490	20.89 ± 15.67	0.10 ± 2.08	0.964	-3.98	4.18
	Presence	40	20.80 ± 12.40				
Area 5 (Inferior)	No presence	356	20.22 ± 15.52	- 2.34 ± 1.41	0.015	-5.10	0.42
	Presence	174	22.25 ± 15.20				

3.2 Analysis of the relationship between corneal staining and tear meniscus height

There was found a statistical difference in the TMH parameter between groups when the sample was grouped by Oxford Grade (ANOVA: p = 0.006; Table 4). The relationship between the tear volume represented by TMH and the location of the staining was analysed area by area. In each analysis, the sample was split by the presence or not of corneal staining in the studied area, and the difference in the TMH parameter was assessed. There was found a statistical difference in TMH value between participants split by presence or not of staining when corneal damage was located in the central (impaired t-test; p = 0.007), the nasal (impaired t-test; p < 0.001) or inferior areas (independent t-test; p = 0.015) (Table 5).

Table 4. Descriptive statistics and differences (ANOVA) in the TMH between participants grouped by Oxford Grade. Oxford Grade is a no-dimensional parameter. TMH values are provided in mm. TMH = Tear Meniscus Height. SD = Standard Deviation.

		TMH		
Oxford Grade	**n**	**Mean**	**SD**	
0	346	0.171	0.058	0.001
1	106	0.168	0.060	
2	57	0.155	0.070	
3	16	0.123	0.048	
4	5	0.085	0.015	

Table 5. Differences (paired t-test) and 95% limits of agreement between subjects grouped by the presence or not of staining in each corneal area. Oxford Grade is a no-dimensional parameter. TMH values are provided in mm. TMH = Tear Meniscus Height. SD = Standard Deviation. 95% LoAs = 95% Limits of Agreement.

			TMH				
Area	**Presence of staining**	**n**	**Mean ± SD**	**Mean Difference ± SD**	**p**	**95% LoA**	
						Lower	**Upper**
Area 1 (Central)	No presence	478	0.169 ± 0.060	0.023 ± 0.009	0.007	0.005	0.041
	Presence	52	0.145 ± 0.064				
Area 2 (Nasal)	No presence	437	0.171± 0.060	0.028 ± 0.007	< 0.001	0.014	0.042
	Presence	93	0.143 ± 0.043				
Area 3 (Temporal)	No presence	464	0.167 ± 0.057	0.002 ± 0.007	0.804	-0.012	0.016
	Presence	66	0.165 ± 0.079				
Area 4 (Superior)	No presence	490	0.167 ± 0.060	0.009 ± 0.009	0.347	-0.009	0.027
	Presence	40	0.158 ± 0.056				
Area 5 (Inferior)	No presence	356	0.171 ± 0.059	0.014 ± 0.005	0.013	0.004	0.024
	Presence	174	0.157 ± 0.061				

4. CONCLUSION

In the present study, two different parameters or classifications of the corneal staining in a big sample were compared with reference characteristics in the dry eye diagnosis: patient's symptoms and tear film volume. Those parameters were reordered and analysed in a further session by masked observers as there was demonstrated there is no difference in assigned grade between static and dynamic images [26]. All the analysed were performed by optometrists with high expertise in the field.

A difference in the symptomatic complains were found between subjects with different corneal damage status (Table 2); higher grades of damage are related to dry eye complains. A similar trend was found when in the stratification by damage level the TMH meniscus was used: lower tear meniscus heights (indicating a decrease in the tear meniscus total volume) are inversely related with the corneal damage status (Table 4); similar results were found by previous authors [27-29]. On the other hand, CCLRU classifications use five areas to set where the staining was located [30-32]. It was found that the relationships previous found in the present study between corneal damage with symptomatology and tear volume are influenced by the area where the damage is located (Tables 3 and 5): nasal and inferior areas seem to have an important role in the symptomatology and volume in a relationship with the damage. The present study showed that there is a relationship between corneal damage grade and corneal zones with dry eye symptomatology and tear film volume.

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