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# Is contact lens discomfort related to meibomian gland morphology?

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## ABSTRACT

*Purpose:* To examine the relationship between contact lens (CL) discomfort and meibomian gland (MG) morphology assessed by a semi-objective software in subjects without an alteration of MG function (meibum quality and expressibility).

*Methods*: Nineteen symptomatic (CLDEQ-8  $\geq$  12) CL wearers, 19 asymptomatic (CLDEQ-8 < 12) wearers, and 22 non-wearers were recruited. Upper and lower eyelid meibography images were taken and the following parameters were analysed using a semi-objective software in the central 2/3 of each eyelid: number of MG, number of partial MG, percentage of MG loss and percentage of tortuosity. One-way ANOVA or Kruskal-Wallis H test were used for comparisons among groups. The relationships between CLDEQ-8 and MG morphology parameters were analysed using the Spearman correlation coefficient and multivariable linear regression models.

*Results:* No significant differences were found among groups in the MG morphology of the upper or lower eyelids. In all CL wearers, a significant correlation with CLDEQ-8 was found in the upper eyelid for the number of MG (rho = 0.47, p = 0.003). In symptomatic wearers, significant correlations with CLDEQ-8 were found in the lower eyelid for the number of partial MG (rho = 0.49, p = 0.03) and the percentage of partial MG (rho = 0.61, p = 0.005). In all CL wearers, multivariable models were fitted to explain CLDEQ-8 score including the number of MG, the number of partial MG and the percentage of MG loss from the lower eyelid ( $R^2 = 0.19$ ; p = 0.007), and the number of MG from the upper eyelid ( $R^2 = 0.19$ ; p = 0.001). In symptomatic wearers, a model was fitted including the percentage of MG loss from the lower eyelid ( $R^2 = 0.30$ ; p = 0.016).

*Conclusions:* Alterations of MG morphology, without clinically apparent alteration of MG function, can be involved in causing CL discomfort and influence the degree of symptoms. The differences in findings between eyelids indicate the need to monitor both eyelids, especially the lower one, in CL wearers.

# 1. Introduction

Contact lens (CL) discomfort is a condition suffered by 31–58 % of wearers [1], and is the main reason for permanent discontinuations at a rate that has been variously reported as between 12 % and 51 % [2]. The Tear Film & Ocular Surface Society Workshop on Contact Lens Discomfort defines CL discomfort as "a condition characterized by episodic or persistent adverse ocular sensations related to lens wear, either with or without visual disturbance, resulting from reduced compatibility between the contact lens and the ocular environment, which can lead to decreased wearing time and discontinuation of contact lens wear" [3]. Some of the causes of CL discomfort that have been

suggested so far are tear film instability [4,5], increased tear film evaporation [4–7], inflammation [8–10], dewetting of the CL surface [7], lid-wiper epitheliopathy, and alterations of the meibomian glands (MG) [11]. MG alterations and lid-wiper epitheliopathy are the two issues that show the strongest link to CL discomfort [11].

MG are sebaceous glands located in the tarsal plates of the eyelids that synthesize and secrete mainly lipids into the tear film. These lipids from the lipid layer play a fundamental role in the stability of the tear film, reducing the evaporation of the aqueous component, preserving a clear optical surface, and forming a barrier to prevent contamination [12–15]. Consequently, an alteration of the MG function has the potential to affect ocular surface homeostasis leading to dry eye symptoms

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#### [16].

MG morphology is habitually evaluated through subjective grading scales [5,7,12,17–19]. These scales have a lower sensitivity and more inter-observer and intra-observer variability than semi-objective or objective strategies [18,20,21]. In recent years, semi-objective and objective analysis, such as those performed with ImageJ or Phoenix software, have been used to assist the observer in quantifying the morphological parameters of the MG more accurately and objectively [20,22].

Long-term CL wear has been reported to alter both, MG function [11,12,17,18,23–25] and MG morphology [12,17,18,25]. A loss of MG function has a known negative impact on the tear film, being one of the main causes of ocular discomfort in CL wearers [12,16,26]. However, it is not clear whether an isolated alteration of MG morphology, i.e., one that occurs without an apparent clinical impact on MG function (meibum quality and expressibility), may cause discomfort. Indeed, changes in MG morphology have been reported both with [18,27] and without [28] alterations in meibum quality and expressibility, suggesting that morphological changes could induce functional changes that are currently unobservable with existing techniques. For this reason, the aim of this study is to analyse whether an alteration of MG morphology itself, assessed by a semi-objective software, can induce ocular discomfort in CL wearers without an apparent clinical alteration of MG function (meibum quality and expressibility).

## 2. Methods

This was a prospective, observational, case-control study approved by the University of Valladolid Ethics Committee (Valladolid, Spain). The study complied with the tenets of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practices. Participants were informed about the study and written consent was obtained prior to their participation in the study.

### 2.1. Participant sample

Three groups of participants were recruited: 1) symptomatic CL wearers, 2) asymptomatic CL wearers and 3) non-CL wearers. The inclusion criterion for CL wearers was being soft CL wearers for at least 6 months prior to the study visit. Participants with symptoms of CL discomfort were considered to have a Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8) score  $\geq 12$  [29]. Non-CL wearers should have no previous history of CL wear.

The exclusion criteria for all participants were: age under 18 years, extended or continuous CL wear, rigid gas-permeable CL wear, active ocular disease, history of a previous ocular surgery, use of topical medication other than artificial tears, and systemic disease that contraindicated CL wear. Additionally, participants with dry eye disease or abnormal MG function were excluded. Participants were considered to have dry eye disease when the Ocular Surface Disease Index (OSDI) score was  $\geq 13$  and at least two of the following conditions were present (in at least one eye): fluorescein tear break-up time (TBUT)  $\leq 7$  s, fluorescein corneal staining extension  $\geq$  grade 2 according to the Cornea and Contact Lens Research Unit (CCLRU) scale in any area of the cornea, and Schirmer I test without anaesthesia  $\leq 5$  mm after 5 min [30]. MG function was considered abnormal when the quality and expressibility of lipid secretion were > 1 according to the Shimazaki et al. scale [31–33].

### 2.2. Clinical examination

Participants were evaluated in a single visit. CL wearers were instructed not to wear their CLs for at least 24 h prior to the visit. Firstly, clinical history was taken and then the following clinical evaluation was performed.

#### 2.2.1. Symptom evaluation

All participants were instructed to complete the OSDI questionnaire considering the symptoms they had suffered without CLs in the last week. The OSDI questionnaire consists of 12 questions that assess symptoms related to dry eye and their impact on vision [34]. The OSDI score ranges from 0 to 100, with a diagnostic cut-off  $\geq$  13 [35]. Moreover, CL wearers filled out the CLDEQ-8 considering the symptoms they had experienced while wearing CLs in the last two weeks. The CLDEQ-8 is an 8-item questionnaire that evaluates the symptoms of CL discomfort. The diagnostic cut-off for the CLDEQ-8 is  $\geq$  12 (total range 1–37) [29].

## 2.2.2. Clinical signs

TBUT and corneal staining were evaluated using sodium fluorescein strips (BioFluoro, Tiedra farmacéutica S.L, Madrid, Spain), a cobalt blue filter on a slit-lamp biomicroscope (SL-D7, Topcon Corporation, Tokyo, Japan) and a Wratten #12 yellow filter (Eastman Kodak Company, New York, USA). Three TBUT measures were taken, and the average was calculated. CCLRU grading scale (0–4) was used for assessing the extent of central, superior, inferior, nasal and temporal corneal staining, and the sum of the five areas was calculated (0–20) [36]. Schirmer I test (Tear Strips, Care Group, Gujarat, India) without anaesthesia was carried out to evaluate tear production.

Regarding MG function, quality and expressibility of meibum secretion was evaluated by applying digital pressure on the eyelids and was graded according to the following scale: 0 = clear meibum, easily expressed; 1 = cloudy meibum, easily expressed; 2 = cloudy meibum expressed with moderate pressure; 3 = meibum not expressible, even with hard pressure [31–33].

## 2.2.3. Meibography

Images of tarsal conjunctiva of the upper and lower eyelids were taken using a custom-made infrared non-contact meibography system to evaluate MG morphology. The eyelids were everted ensuring that at least the central 2/3 area of each eyelid was exposed. A slit lamp, an infrared device video camera (SUNLUXY® 420TVL CCTV Camera, model SL-C221, China) and a video transmitter (GRABSTER AV 350 MX and MAGIX Video easy, Terratec, Germany) were used to capture MG images. Images were then processed (contrast enhanced, Fig. 1) and analysed using ImageJ software, whose repeatability and reliability have been demonstrated [20,22,37]. First, the central 2/3 area of the evelid was determined. The total horizontal length of the evelid was measured in pixels, then 1/6 of that length was traced from the medial and lateral canthi of the evelid toward the centre to obtain the central 2/ 3 area. The following parameters were then analysed in this area by a masked observer: number of MG, number of partial MG, percentage of MG tortuosity and percentage of MG loss (Fig. 2). Partial MG were considered to be those that did not reach the fornix (Fig. 1). MG tortuosity was estimated as the percentage of tortuous MG in relation to the number of MG. MG were considered tortuous when the duct had at least 1 curvature (Fig. 1) [38].

## 2.3. Statistical analysis

The R statistical package (version 4.1.2) was used to perform the statistical analysis of the data. Sample size was estimated to detect a significant difference of at least 10 % in the percentage of MG loss using the analysis of variance (ANOVA) for 3 groups and considering the standard deviation of CL wearers reported by Pucker et al. (10.6) [39]. Establishing a significance level of 0.05 and a statistical power of 80 %, at least 18 participants were needed in each study group. Both eyes were evaluated, although one eye was considered for analysis. The most symptomatic eye was chosen for the symptomatic CL wearers (it was considered on the basis of the participant's response), and a random eye was chosen for the groups of asymptomatic CL wearers and non-CL wearers.

For comparisons between two groups, independent samples t-test



Fig. 1. Partial (yellow arrows), complete (purple arrows), tortuous (blue arrows) and non-tortuous (black arrows) meibomian glands are represented. Unprocessed images are shown on the left, and images processed with ImageJ software are shown on the right.



Fig. 2. Example of the measurement of the percentage of meibomian gland (MG) loss in the upper eyelid with ImageJ software. The yellow solid line with square markers represents the MG area, and the black dashed line represents the area of MG loss.

was used for normally distributed quantitative variables and Mann Whitney *U* test was employed for non-normally distributed quantitative variables. For comparisons among three groups, quantitative variables were analysed using one-way ANOVA (when normality was assumed) and Kruskal-Wallis H test (when normality could not be assumed), while ordinal and nominal variables were assessed with Kruskal-Wallis H and Chi-square tests, respectively. Post-hoc pairwise comparisons were assessed by Tukey test for normally distributed quantitative variables, or the Nemenyi test for non-normally distributed quantitative variables and ordinal variables. P-values  $\leq 0.05$  were considered statistically significant.

The relationship between CL discomfort (CLDEQ-8 score) and each MG morphology parameter of each eyelid was analysed using the Spearman correlation coefficient (rho). In addition, multivariable linear regression models were fitted for each eyelid including the CLDEQ-8 as the dependent variable and the four MG morphology parameters as the independent variables. A backward elimination method using a p-value

threshold of 0.05 was used for variable selection. The lack of multicollinearity was checked by calculating the variance inflation factor (VIF < 5), and the assumptions of linearity, normality, homoscedasticity, and lack of outliers were checked using the residuals of each fitted model. Correlations and multivariable regression models were performed for all CL wearers, as well as for symptomatic CL wearers separately. P-values  $\leq$  0.05 were considered statistically significant.

## 3. Results

### 3.1. Participants

Sixty volunteer participants (38 females and 22 males) with a mean age of  $23.8 \pm 6.3$  (range 18–58) years were recruited and divided into three groups: 19 symptomatic CL wearers, 19 asymptomatic CL wearers and 22 non-CL wearers. Descriptive data for the study groups are summarized in Table 1.

#### Table 1

Descriptive data for the study groups.

Variables	Symptomatic CL wearers	Asymptomatic CL wearers	Non-CL wearers	P-value
Age (years)	$22.5\pm4.8$	$24.6 \pm 5.4$	$24.2 \pm 8.0$	0.210
	(18.0-35.0)	(19.0–39.0)	(19.0-58.0)	
Sex (%female /	73.7 / 26.3	57.9 / 42.1	59.1 / 40.9	0.525
%male)				
Duration of CL	$5.9\pm3.9$	$8.2\pm4.5$	_	0.117
wear (years)	(0.5 - 15.0)	(0.7 - 20.0)		
CLDEQ-8	$21.8 \pm 4.9$	$\textbf{7.2} \pm \textbf{2.7}$	_	< 0.001
(range, 1–37)	(14.0-30.0)	(0.0-11.0)		
OSDI (range,	$14.2\pm9.9$	$6.1\pm5.4$	$\textbf{6.5} \pm \textbf{6.4}$	0.003
0–100)	(2.3–38.6)	$(0.0-18.2)^{a}$	$(0.0-22.0)^{b}$	
TBUT (s)	$9.4\pm 6.0$	$12.0\pm6.1$	$12.6\pm7.2$	0.222
	(3.7–27.3)	(4.0–29.0)	(3.3 - 27.0)	
Corneal staining	$0.4\pm0.7$	$0.7\pm1.0$	$0.4\pm0.7$	0.697
(range, 0-20)	(0.0 - 2.0)	(0.0-3.0)	(0.0 - 2.0)	
Schirmer test	$19.0\pm11.2$	$23.3 \pm 11.6$	$24.7 \pm 11.0$	0.540
(mm)	(5.0-36.0)	(7.0-35.0)	(3.0-37.0)	
Quality and	0 [0,1]	0 [0,1]	0 [0,1]	0.857
expressibility				
of lipid				
secretion				
(range, 0–3)				

Numerical variables are presented as mean  $\pm$  standard deviation (minimum-maximum), ordinal variables are presented as median [interquartile range], and nominal variables are presented as percentage. <sup>a</sup> P-value = 0.004 compared to symptomatic CL wearers. <sup>b</sup> P-value = 0.003 compared to symptomatic CL wearers. CL: contact lens; CLDEQ-8: Contact Lens Dry Eye Questionnaire-8; OSDI: Ocular Surface Disease Index; TBUT: tear break-up time.

## 3.2. MG morphology

Significant differences were found in the number of MG in the lower eyelid, with the group of symptomatic CL wearers having the least number of MG (Table 2). However, no significant differences were found in post-hoc pairwise comparisons ( $p \geq 0.062$ ). Regarding the upper eyelid, borderline differences were obtained in the number of MG and the number of partial MG, with higher values in the group of symptomatic CL wearers.

#### 3.3. Relationship between CL discomfort and MG morphology

A significant positive correlation was found between the CLDEQ-8 and the number of MG in the upper eyelid considering all CL wearers

### Table 2

Parameters of meibomian gland (MG) morphology.			
Variables	Symptomatic CL wearers	Asymptomatic CL wearers	Non-CL wearers

	CL wearers	CL wearers	wearers	value
Lower eyelid				
Number of MG	$10.2\pm2.0$	$11.7\pm2.0$	$11.6\pm2.3$	0.041
	(7.0–15.0)	(9.0–17.0)	(8.0–17.0)	
Number of	$3.6\pm3.4$	$3.9\pm3.2$	$3.3\pm3.6$	0.451
partial MG	(0.0–15.0)	(0.0-13.0)	(0.0–14.0)	
Percentage of	$10.0\pm7.0$	$13.7\pm13.4$	$\textbf{8.7} \pm \textbf{5.7}$	0.577
MG loss	(0.9–30.7)	(1.6-57.1)	(1.4 - 24.7)	
Percentage of	$21.8 \pm 16.0$	$17.5\pm14.3$	$\textbf{26.4} \pm \textbf{22.6}$	0.305
MG	(0.0–55.5)	(0.0-41.7)	(0.0–77.8)	
tortuosity				
Upper eyelid				
Number of MG	$14.8\pm2.3$	$12.8\pm2.8$	$13.9\pm2.6$	0.066
	(11.0–19.0)	(8.0–18.0)	(8.0–19.0)	
Number of	$11.9 \pm 2.9$	$9.9\pm3.7$	$\textbf{9.14} \pm \textbf{4.2}$	0.056
partial MG	(7.0–17.0)	(3.0–16.0)	(0.0–16.0)	
Percentage of	$17.3\pm6.4$	$19.5\pm10.7$	$15.9 \pm 14.3$	0.232
MG loss	(6.4–28.9)	(5.1-42.8)	(1.6 - 70.2)	
Percentage of	$64.9 \pm 20.8$	$\textbf{70.6} \pm \textbf{22.8}$	$60.6 \pm 19.0$	0.314
MG	(35.3–94.1)	(25.0–100.0)	(12.5 - 90.9)	
tortuosity				

Data are presented as mean  $\pm$  standard deviation (minimum-maximum).

(rho = 0.47, p = 0.003). In the symptomatic CL wearers, the CLDEQ-8 significantly correlated with the number of partial MG (rho = 0.49, p = 0.034) and the percentage of MG loss (rho = 0.61, p = 0.005), both in the lower eyelid. No other significant correlations were found (Table 3).

Linear regression models were fitted for all CL wearers in the lower  $(R^2 = 0.19; p = 0.007)$  and upper  $(R^2 = 0.19; p = 0.001)$  eyelids as well as for the symptomatic wearers in the lower eyelid  $(R^2 = 0.30; p = 0.016)$ . However, none of the variables were significant during variable selection for symptomatic wearers in the upper eyelid, then, no model could be fitted. The coefficients of the models constructed for all CL wearers and symptomatic wearers are shown in Table 4.

#### 4. Discussion

Alterations in MG function can affect the tear film, which may trigger symptoms of ocular discomfort [16]. Many authors agree on the impact of CL wear on the alteration of MG function and the consequent development of ocular symptomatology [11,18,23–25]. However, there is controversy about the relationship between the changes of MG morphology and discomfort in CL wearers. Additionally, many of the studies to date have analysed MG morphology using subjective grading scales, which have limited sensitivity and high intra- and inter-observer variability [18,20,21]. Therefore, the present study evaluated the relationship between CL discomfort and MG morphology, as assessed by semi-objective software, in participants without an apparent alteration of MG function (meibum quality and expressibility).

The results of this study showed differences in the number of MG of the lower eyelid when comparing the three study groups; however, significant differences disappeared in the post-hoc pairwise comparisons. In addition, no significant differences were found in MG loss, number of partial MG or tortuosity of the upper or lower eyelids, suggesting that CL wear itself does not impact MG morphology. This lack of significant differences between non-CL wearers and both groups of CL wearers in any of the MG morphology parameters agrees with some reports in the scientific literature. These studies analysed the MG loss with ImageJ software and subjective grading scales, tortuosity using a subjective scale, and density by counting the number of MG in 1 cm, finding no effect of CL wear on these parameters [24,39]. On the opposite, other studies have detected higher grades of MG loss in CL wearers [12,17,18,25]. Thus, given the discrepancies between the various studies and the lack of significant results in the present work, the effect of CL wear on MG morphology remains unclear.

In addition, the lack of significant differences between symptomatic and asymptomatic CL wearers in the four parameters of MG morphology has been reported in the literature. Specifically, several studies analysing MG morphology using subjective grading scales found no significant effect of MG loss, or tortuosity, of the upper and lower eyelids on either CL discomfort, or dropouts due to discomfort [7,19]. Conversely,

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Spearman correlation coefficients between the Contact Lens Dry Eye Questionnaire-8 and the MG morphology parameters.

Variables	All CL wearers	Symptomatic CL wearers
Lower eyelid		
Number of MG	-0.20 (p = 0.229)	0.10 (p = 0.680)
Number of partial MG	-0.02 (p = 0.903)	0.49 (p = <b>0.034</b> )
Percentage of MG loss	-0.05 (p = 0.765)	0.61 (p = <b>0.005</b> )
Percentage of MG tortuosity	0.12 (p = 0.454)	-0.22 (p = 0.370)
Upper eyelid		
Number of MG	0.47 (p = <b>0.003</b> )	0.02 (p = 0.938)
Number of partial MG	0.26 (p = 0.115)	-0.27 (p = 0.265)
Percentage of MG loss	-0.18 (p = 0.278)	-0.28 (p = 0.253)
Percentage of MG tortuosity	-0.12 (p = 0.468)	0.25 (p = 0.303)

Data show the Spearman correlation coefficient (rho) and its corresponding p-value. CL: contact lens; MG: meibomian gland.

#### Table 4

Coefficients of the multivariable linear regression models for all contact lens (CL) wearers and symptomatic CL wearers.

Variables	Unstandardized coefficients (95 % CI)	Standardized coefficients (95 % CI)	P-value	
All CL wearers, lower eyelid ( $R^2 = 0.19$ ; $p = 0.007$ )				
Intercept	34.66 (21.23/48.08)		0.001	
Number of MG	-1.93 (-3.19/-0.679)	-4.27 (-7.04/-1.50)	0.004	
Number of partial MG	2.61 (1.22/4.00)	8.81 (4.12/13.5)	0.001	
Percentage of	-0.747 (-1.15/-0.35)	-6.94 (-10.64/	0.001	
MG loss	2	-3.24)		
All CL wearers, upper eyelid ( $R^2 = 0.19$ ; $p = 0.001$ )				
Intercept	-4.07 (-17.39/9.24)		0.539	
Number of MG	1.34 (0.40/2.29)	1.24 (1.06/6.09)	0.007	
Symptomatic CL wearers, lower eyelid ( $R^2 = 0.30$ ; $p = 0.016$ )				
Intercept	18.00 (14.34/21.67)		<0.001	
Percentage of MG loss	0.38 (0.08/0.69)	2.70 (0.57/4.82)	0.016	

CI: confidence interval; MG: meibomian gland.

Siddireddy et al. [5] observed greater MG loss in symptomatic CL wearers compared to asymptomatic CL wearers. These discrepancies might be explained by alterations in MG function which, although undetected by traditional clinical methods, are due to morphological changes. This suggests the hypothesis that a change of MG morphology, without clinically apparent alteration of MG function, can be a potential cause for CL discomfort.

The findings of the present study did show some significant relationships between CL discomfort and MG morphology. Nonetheless, some of the results found appear to be unhelpful. Particularly, a higher number of MG in the upper eyelid was associated with a higher CLDEQ-8 score, in the whole group of CL wearers. However, when symptomatic wearers were analyzed separately, this counterintuitive result disappeared. Given the lack of, or minimal, symptoms expected in the asymptomatic wearers, whose range of CLDEQ-8 scores varied between 0 and 11, the resulting data might be the result of chance and so, should be interpreted with caution.

In the lower eyelid, a linear combination of MG morphology parameters (number of MG, number of partial MG and percentage of MG loss) appears more useful for explaining CLDEQ-8 score in all wearers. It may also indicate that the morphology of lower eyelid is more likely to drive the pre-clinical changes that affect discomfort responses.

For symptomatic wearers, CLDEQ-8 showed univariate positive correlations with the number of partial MG and the percentage of MG loss in the lower eyelid, but only the percentage of MG loss remained in the multivariable regression model. The reason why the number of partial MG was not included in the model was likely to be that it quantifies a similar characteristic to percentage MG loss, with the latter being more detailed.

Other studies have also reported relationships between ocular symptomatology and MG morphology. In particular, a positive correlation has been reported between ocular symptoms, assessed by the OSDI questionnaire, and MG loss in CL wearers and/or non-CL wearers [24,40–42]. It also appears relevant that the symptomatology of CL wearers is known to improve with MG treatments, such as eyelid hygiene and intense pulsed light, with some authors even reporting that MG loss (evaluated by software and subjective grading scales) decreases in such circumstances [43–45]. All these findings support the idea that CL-related symptomatology is associated with MG loss, at least.

It is also interesting to note that the relationship between MG morphology and CL discomfort was different between eyelids, with lower lid morphology being the best predictor of symptomatology. Crespo-Treviño et al. also showed no differences in upper lid, MG morphology between healthy and dry eye disease subjects [46] and other authors have reported MG loss to be higher in lower eyelids than upper eyelids [47–49]. As a possible explanation for the differences

between eyelids, Eom et al. [47] hypothesized that pronounced movements of upper eyelids during blinking facilitate the secretion of meibum, which could prevent MG loss. Conversely, greater changes in the upper eyelid have been found and attributed to increased friction between the lid and ocular and CL surfaces relative to the lower eyelid [5,17].

Given this uncertainty, both eyelids should be assessed, since the morphology may differ [28,50] and in CL wearers, the lower eyelid may require more detailed observation because of its relationship with ocular discomfort.

The present study has some limitations. It had a cross-sectional design which did not allow investigation of the cause-effect relationship between CL discomfort and MG alterations. Longitudinal studies in neophytes, before and after CL wear, are needed, although the relationship may be complex as it is not possible to predict the development of CL discomfort. Additionally, the mean age of the participants was younger than that of CL wearers in general [51]. This may be a consequence of excluding those with evident alteration of MG function, which is known to increase with age [13,15]. On the other hand, this will have tended to diminish the inclusion of age-related confounding risk factors, such as MG dysfunction [52]. No differences in age, gender or years of CL wear were found among groups.

The most symptomatic eye was chosen for analysis, based on the assumption that this would mainly influence the global subjective opinion as measured by questionnaires (which consider both eyes together). This influence was considered irrelevant for asymptomatic wearers, given that little or no symptomatology is expected. Nonetheless, it is remarkable that 17 of the 19 symptomatic wearers did not indicate a preference and the study eye was then selected randomly. Therefore, the effect of this selection is likely to be minimal.

In conclusion, the results of this study suggest that an alteration of the MG morphology alone, i.e., without clinically apparent alteration of MG function (meibum quality and expressibility), can potentially be responsible for CL discomfort. Further, once discomfort appears, MG loss may play a role in the degree of CL-related symptoms. MG alteration of the lower and upper eyelids may be different and while it is important to monitor both eyelids, in CL wearers the lower eyelid may be particularly useful in showing changes that lead to the onset of symptoms.

## **Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### References

- [1] Stapleton F, Bakkar M, Carnt N, Chalmers R, Vijay AK, Marasini S, et al. CLEAR Contact lens complications. Contact Lens Anterior Eye 2021;44:330–67. https:// doi.org/10.1016/j.clae.2021.02.010.
- [2] Dumbleton K, Caffery B, Dogru M, Hickson-Curran S, Kern J, Kojima T, et al. The TFOS International Workshop on Contact Lens Discomfort: Report of the Subcommittee on Epidemiology. Invest Ophthalmol Vis Sci 2013;54(11): TFOS20–36. https://doi.org/10.1167/iovs.13-13125.
- [3] Nichols KK, Redfern RL, Jacob JT, Nelson JD, Fonn D, Forstot SL, et al. The TFOS International Workshop on Contact Lens Discomfort: Report of the Definition and Classification Subcommittee. Invest Ophthalmol Vis Sci 2013;54(11):TFOS14-9. https://doi.org/10.1167/iovs.13-13074.
- [4] Kojima T, Matsumoto Y, Ibrahim OMA, Wakamatsu TH, Uchino M, Fukagawa K, et al. Effect of controlled adverse chamber environment exposure on tear functions in silicon hydrogel and hydrogel soft contact lens wearers. Invest Ophthalmol Vis Sci 2011;52(12):8811–7. https://doi.org/10.1167/iovs.10-6841.
- [5] Siddireddy JS, Vijay AK, Tan J, Willcox M. The eyelids and tear film in contact lens discomfort. Cont Lens Anterior Eye 2018;41:144–53. https://doi.org/10.1016/J. CLAE.2017.10.004.
- [6] Guillon M, Maissa C. Contact lens wear affects tear film evaporation. Eye Contact Lens 2008;34:326–30. https://doi.org/10.1097/ICL.0B013E31818C5D00.
- [7] Nichols JJ, Sinnott LT. Tear film, contact lens, and patient-related factors associated with contact lens-related dry eye. Invest Ophthalmol Vis Sci 2006;47: 1319–28. https://doi.org/10.1167/IOVS.05-1392.

- [8] López-de la Rosa A, González-García MJ, Calonge M, Enríquez-de-Salamanca A. Tear inflammatory molecules in contact lens wearers: a literature review. Curr Med Chem 2020;27:523–48. https://doi.org/10.2174/0929867326666190409152921.
- [9] López-de la Rosa A, Fernández I, García-Vázquez C, Arroyo-Del Arroyo C, González-García MJ, Enríquez-de-Salamanca A. Conjunctival neuropathic and inflammatory pain-related gene expression with contact lens wear and discomfort. Ocul Immunol Inflamm 2019;29:587–606. https://doi.org/10.1080/ 09273948.2019.1690005.
- [10] Elgin CY, İskeleli G, Talaz S, Akyol S. Comparative analysis of tear film levels of inflammatory mediators in contact lens users. Curr Eye Res 2016;41:441–7. https://doi.org/10.3109/02713683.2015.1037001.
- [11] Nichols JJ, Willcox MDP, Bron AJ, Belmonte C, Ciolino JB, Craig JP, et al. The TFOS International Workshop on contact lens discomfort: executive summary. Invest Ophthalmol Vis Sci 2013;54(11):TFOS7–13. https://doi.org/10.1167/ iovs.13-13212.
- [12] Villani E, Ceresara G, Beretta S, Magnani F, Viola F, Ratiglia R. In vivo confocal microscopy of meibomian glands in contact lens wearers. Invest Ophthalmol Vis Sci 2011;52:5215–9. https://doi.org/10.1167/IOVS.11-7427.
- [13] Nichols KK, Foulks GN, Bron AJ, Glasgow BJ, Dogru M, Tsubota K, et al. The international workshop on meibomian gland dysfunction: executive summary. Invest Ophthalmol Vis Sci 2011;52(4):1922–9. https://doi.org/10.1167/iovs.10-6997a.
- [14] Knop E, Knop N, Schirra F. Meibomian glands. Part II: physiology, characteristics, distribution and function of meibomian oil. Ophthalmologe 2009;106:884–92. https://doi.org/10.1007/S00347-009-2019-9.
- [15] Obata H. Anatomy and histopathology of human meibomian gland. Cornea 2002; 21:S70–4. https://doi.org/10.1097/01.ICO.0000263122.45898.09.
- [16] Arita R, Fukuoka S, Morishige N. Meibomian gland dysfunction and contact lens discomfort. Eye Contact Lens 2017;43:17–22. https://doi.org/10.1097/ ICL.000000000000351.
- [17] Arita R, Itoh K, Inoue K, Kuchiba A, Yamaguchi T, Amano S. Contact lens wear is associated with decrease of meibomian glands. Ophthalmology 2009;116:379–84. https://doi.org/10.1016/j.ophtha.2008.10.012.
- [18] Alghamdi WM, Markoulli M, Holden BA, Papas EB. Impact of duration of contact lens wear on the structure and function of the meibomian glands. Ophthalmic Physiol Opt 2016;36:120–31. https://doi.org/10.1111/OPO.12278.
- [19] Pucker AD, Jones-Jordan LA, Kunnen CME, Marx S, Powell DR, Kwan JT, et al. Impact of meibomian gland width on successful contact lens use. Cont Lens Anterior Eye 2019;42(6):646–51. https://doi.org/10.1016/j.clae.2019.06.004.
- [20] Pult H, Riede-Pult B. Comparison of subjective grading and objective assessment in meibography. Cont Lens Anterior Eye 2013;36:22–7. https://doi.org/10.1016/J. CLAE.2012.10.074.
- [21] Ngo W, Srinivasan S, Schulze M, Jones L. Repeatability of grading meibomian gland dropout using two infrared systems. Optom Vis Sci 2014;91:658–67. https:// doi.org/10.1097/OPX.0000000000279.
- [22] Garza-Leon M, Gonzalez-Dibildox A, Ramos-Betancourt N, Hernandez-Quintela E. Comparison of meibomian gland loss area measurements between two computer programs and intra-inter-observer agreement. Int Ophthalmol 2020;40:1261–7. https://doi.org/10.1007/S10792-020-01292-W.
- [23] Ong BL, Larke JR. Meibomian gland dysfunction: some clinical, biochemical and physical observations. Ophthalmic Physiol Opt 1990;10:144–8. https://doi.org/ 10.1111/J.1475-1313.1990.TB00968.X.
- [24] Machalińska A, Zakrzewska A, Adamek B, Safranow K, Wiszniewska B, Parafiniuk M, et al. Comparison of morphological and functional meibomian gland characteristics between daily contact lens wearers and nonwearers. Cornea 2015; 34:1098–104. https://doi.org/10.1097/ICO.000000000000511.
- [25] Pucker AD, Jones-Jordan LA, Marx S, Powell DR, Kwan JT, Sickenberger W, et al. The role of soft contact lens wear on meibomian gland morphology and function. Eye Contact Lens 2019;45(4):276–7. https://doi.org/10.1097/ ICL.000000000000598
- [26] Llorens-Quintana C, Rico-Del-Viejo L, Syga P, Madrid-Costa D, Robert D. Meibomian gland morphology: the influence of structural variations on gland function and ocular surface parameters. Cornea 2019;38:1506–12. https://doi.org/ 10.1097/ICO.00000000002141.
- [27] Ji YW, Lee J, Lee H, Seo KY, Kim EK, Kim TI. Automated measurement of tear film dynamics and lipid layer thickness for assessment of non-sjögren dry eye syndrome with meibomian gland dysfunction. Cornea 2017;36:176–82. https://doi.org/ 10.1097/ICO.00000000001101.
- [28] Rico-del-Viejo L, Benítez-del-Castillo JM, Gómez-Sanz FJ, García-Montero M, Llorens-Quintana C, Madrid-Costa D. The influence of meibomian gland loss on ocular surface clinical parameters. Contact Lens Anterior Eye 2019;42:562–8. https://doi.org/10.1016/J.CLAE.2019.04.004.
- [29] Chalmers RL, Keay L, Hickson-Curran SB, Gleason WJ. Cutoff score and responsiveness of the 8-item Contact Lens Dry Eye Questionnaire (CLDEQ-8) in a Large daily disposable contact lens registry. Contact Lens Anterior Eye 2016;39: 342–52. https://doi.org/10.1016/j.clae.2016.04.005.

- [30] Arroyo-Del Arroyo C, Fernández I, Novo-Diez A, Blanco-Vázquez M, López-Miguel A, González-García MJ. Contact lens discomfort management: outcomes of common interventions. Eye Contact Lens 2021;47:256–64. https://doi.org/ 10.1097/ICL.000000000000727.
- [31] Shimazaki J, Sakata M, Tsubota K. Ocular surface changes and discomfort in patients with meibomian gland dysfunction. Arch Ophthalmol 1995;113:1266–70. https://doi.org/10.1001/archopht.1995.01100100054027.
- [32] Tomlinson A, Bron AJ, Korb DR, Amano S, Paugh JR, Ian Pearce E, et al. The International Workshop on Meibomian gland dysfunction: report of the diagnosis subcommittee. Invest Ophthalmol Vis Sci 2011;52:2049. https://doi.org/10.1167/ IOVS.10-6997F.
- [33] Shimazaki J, Goto E, Ono M, Shimmura S, Tsubota K. Meibomian gland dysfunction in patients with Sjögren syndrome. Ophthalmology 1998;105:1485–8. https://doi.org/10.1016/S0161-6420(98)98033-2.
- [34] Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the ocular surface disease index. Arch Ophthalmol 2000;118:615–21. https://doi.org/10.1001/archopht.118.5.615.
- [35] Wolffsohn JS, Arita R, Chalmers R, Djalilian A, Dogru M, Dumbleton K, et al. TFOS DEWS II Diagnostic Methodology report. Ocul Surf 2017;15:539–74. https://doi. org/10.1016/j.jtos.2017.05.001.
- [36] Terry RL, Schnider CM, Holden BA, Cornish R, Grant T, Sweeney D, et al. CCLRU standards for success of daily and extended wear contact lenses. Optom Vis Sci 1993;70:234–43. https://doi.org/10.1097/00006324-199303000-00011.
- [37] Eom Y, Lee JS, Kang SY, Kim HM, Song JS. Correlation between quantitative measurements of tear film lipid layer thickness and meibomian gland loss in patients with obstructive meibomian gland dysfunction and normal controls. Am J Ophthalmol 2013;155:1104–1110.e2. https://doi.org/10.1016/J. AJO.2013.01.008.
- [38] Cabezas M, Cartes C, Flores P, Gauro F, Goya C, Lopez D, et al. Morphological Meibomian Glands Changes in Glaucoma Patients with Chronic Topical Therapy. 2019 ASCRS ASOA Annu. Meet., 2019.
- [39] Pucker AD, Jones-Jordan LA, Li W, Kwan JT, Lin MC, Sickenberger W, et al. Associations with meibomian gland atrophy in daily contact lens wearers. Optom Vis Sci 2015;92:e206–13. https://doi.org/10.1097/OPX.000000000000650.
- [40] Harbiyeli II, Bozkurt B, Erdem E, Özcan HG, Cam B, Sertdemir Y, et al. Associations with meibomian gland loss in soft and rigid contact lens wearers. Cont Lens Anterior Eye 2022;45:101400. https://doi.org/10.1016/J.CLAE.2020.12.005.
- [41] Pult H, Riede-Pult BH. Non-contact meibography: keep it simple but effective. Contact Lens Anterior Eye 2012;35:77–80. https://doi.org/10.1016/J. CLAE.2011.08.003.
- [42] Gu T, Zhao L, Liu Z, Zhao S, Nian H, Wei R. Evaluation of tear film and the morphological changes of meibomian glands in young Asian soft contact lens wearers and non-wearers. BMC Ophthalmol 2020;20:84. https://doi.org/10.1186/ S12886-020-1328-2.
- [43] Arita R, Fukuoka S, Morishige N. Therapeutic efficacy of intense pulsed light in patients with refractory meibomian gland dysfunction. Ocul Surf 2019;17:104–10. https://doi.org/10.1016/J.JTOS.2018.11.004.
- [44] Cheng SN, Jiang FG, Chen H, Gao H, Huang YK. Intense pulsed light therapy for patients with meibomian gland dysfunction and ocular demodex infestation. Curr Med Sci 2019;395:800–9. https://doi.org/10.1007/S11596-019-2108-1.
- [45] Yin Y, Liu N, Gong L, Song N. Changes in the meibomian gland after exposure to intense pulsed light in meibomian gland dysfunction (MGD) patients. Curr Eye Res 2018;43:308–13. https://doi.org/10.1080/02713683.2017.1406525.
- [46] Crespo-Treviño RR, Salinas-Sánchez AK, Amparo F, Garza-Leon M. Comparative of meibomian gland morphology in patients with evaporative dry eye disease versus non-dry eye disease. Sci Rep 2021;11:20729. https://doi.org/10.1038/S41598-021-00122-Y.
- [47] Eom Y, Choi KE, Kang SY, Lee HK, Kim HM, Song JS. Comparison of meibomian gland loss and expressed meibum grade between the upper and lower eyelids in patients with obstructive meibomian gland dysfunction. Cornea 2014;33:448–52. https://doi.org/10.1097/ICO.000000000000092.
- [48] Srinivasan S, Menzies K, Sorbara L, Jones L. Infrared imaging of meibomian gland structure using a novel keratograph. Optom Vis Sci 2012;89:788–94. https://doi. org/10.1097/OPX.0B013E318253DE93.
- [49] Pult H, Riede-Pult BH, Nichols JJ. Relation between upper and lower lids' meibomian gland morphology, tear film, and dry eye. Optom Vis Sci 2012;89: E310–5. https://doi.org/10.1097/OPX.0B013E318244E487.
- [50] Daniel E, Pistilli M, Ying GS, Bunya VY, Massaro-Giordano M, Asbell PA, et al. Association of meibomian gland morphology with symptoms and signs of dry eye disease in the Dry Eye Assessment and Management (DREAM) study. Ocul Surf 2020;18:761–9. https://doi.org/10.1016/J.JTOS.2020.07.014.
- [51] Morgan PB, Woods CA, Tranoudis IG, Efron N, Jones L, Grupcheva CN, et al. International Contact Lens Prescribing in 2020. Contact Lens Spectr 2021;36:32–8.
- [52] Arita R, Itoh K, Inoue K, Amano S. Noncontact infrared meibography to document age-related changes of the meibomian glands in a normal population. Ophthalmology 2008;115:911–5. https://doi.org/10.1016/J. OPHTHA.2007.06.031.