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ORIGINAL ARTICLE

Associations with Meibomian Gland Atrophy in Daily Contact Lens Wearers

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ABSTRACT

Purpose. To determine associations for contact lenses (CLs) and meibomian gland atrophy in a matched-pair study.

Methods. Contact lens wearers (case) and age- and sex-matched non–contact lens (NCL) wearers with no history of CL use (control) were recruited for a multicenter study. All subjects were administered the Ocular Surface Disease Index questionnaire and a comprehensive battery of clinical tests (e.g., tear breakup time, bulbar and limbal redness, meibography, etc.) were performed. Upper and lower eyelid meibomian gland atrophy were graded with both digital meibography (percent gland atrophy) and visual meiboscore methods. Conditional logistic regression analyses were then used to determine relationships among CL use, meibomian gland atrophy, and ocular surface signs and symptoms.

Results. A total of 70 matched pairs were analyzed. The mean (±SD) age of the CL group was 30.6 (±12.4) years, and that of the NCL group was 30.1 (±12.2) years. The subjects were 63% female. The association between CL wear and meiboscore was not significant univariately, but the best-fitting multivariate regression model showed that higher meiboscores were associated with being a CL wearer (odds ratio [OR], 2.45) in a model that included eyelid margin erythema (OR, 0.25) and lissamine green staining (OR, 1.25). Percent gland atrophy was not associated with CL wear in regression analysis ($p = 0.31$).

Conclusions. This study determined inconclusive associations with CLs and meibomian gland atrophy. This study also provided a comprehensive assessment of differences between CL and NCL wearers.

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Key Words: meibomian gland atrophy, contact lenses, meiboscores, meibography, multicenter study, meibomian gland dysfunction, dry eye, Contact Lens Assessment in Symptomatic Subjects (CLASS) Study Group

One potential cause of contact lens (CL) discomfort could be meibomian gland dysfunction because the sequelae of meibomian gland dysfunction likely stem from meibomian gland atrophy, a condition that is known to result in altered tear lipid production.[1,2] This altered lipid production could subsequently result in increased tear evaporation, increased tear osmolality, and dryness symptoms.[3,4] There is currently little information available to prove a direct link between meibomian gland atrophy and CL discomfort. This is largely attributed to a lack of either appropriate study designs or available methods for examining the meibomian glands in a simple and efficient manner. Recently, several studies have presented a patient-friendly clinical method (meibography) for analyzing the meibomian glands that has made it possible to correlate meibomian gland atrophy with clinical tests in large clinical cohorts.[5–7] Although this procedure has been used by a number of investigators to analyze meibomian gland atrophy in the general population, these studies have typically excluded CL wearers.[8–12] Although there have been attempts to analyze this subgroup,[6,13,14] these studies either have failed to fully address how meibomian gland atrophy is related to ocular signs and symptoms in CL wearers (e.g., lack of symptoms data)[6,14] or have included too few subjects to provide generalizable results.[13]

To date, there has yet to be a study aimed at fully describing how meibomian gland atrophy is associated with ocular signs and

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symptoms in CL wearers. Thus, the purpose of this study was to comprehensively evaluate how CL use was associated with meibomian gland atrophy and ocular surface health in a multicenter sample.

METHODS

Study Design

This was a cross-sectional, multisite study conducted at The Ohio State University (Columbus, OH), University of Waterloo (Waterloo, Canada), Marshall B. Ketchum University (Fullerton, CA), Ernst Abbe University of Jena (Jena, Germany), and University of California, Berkeley (Berkeley, CA) between November 2013 and July 2014. Before enrolling subjects, all sites were required to participate in a mandatory investigators' meeting at the University of Waterloo to standardize the test procedures across sites. The study design for a case-control study is generally for case patients to be the ''diseased'' and control subjects to be ''not diseased'' and then to compare the odds ratios (ORs) of the exposures. In the case of meibomian gland atrophy, a priori assessment of disease status was not feasible because of the requirement of photograph reading to determine atrophy, which made recruiting on atrophy impossible. As such, this study recruited case patients based on what would normally be considered the exposure (CL wear) instead of actual cases (gland atrophy). The resultant statistic is the OR, a measure of association. As Bland and Altman have shown, whether calculated in the direction of the disease or in the direction of the exposure, the OR is the same.[15] This relationship was used to determine the association between CL wear and meibomian gland atrophy. Contact lens wearers (case) and age- and sex-matched non–contact lens (NCL) wearers (control) were recruited for a single study visit. Subjects in each group were matched for age (±3 years) and sex to control for known potential differences.[16] All CL wearers were required to have consistently worn CLs for five or more days per week for a minimum of 5 years. Control subjects were only eligible if they had never been prescribed CLs. Each site received its institutional review board approval before enrolling subjects. This study was also conducted in accordance with the Declaration of Helsinki.

Inclusion and Exclusion Criteria

All subjects were prescreened with a scripted phone survey to determine eligibility. Subjects were included if they were 18 years or older and had completed a comprehensive eye examination within the past 12 months. Contact lens wearers were required to have a valid CL prescription. All types of CLs were allowed in this study. Subjects were excluded if they had undergone ocular surgery within the past 12 months, were regular overnight CL wearers, or had a history of severe ocular trauma, scarring, or eyelid abnormalities.[17] Additional exclusions were active ocular infection or inflammation, known hypersensitivity to any diagnostic agents, use of Accutane or prescription eye medications, participation in an investigational drug or device study within the last 30 days, and female subjects who were pregnant or breastfeeding.[17,18] Non–Sjögren syndrome dry eye subjects were allowed to participate because this common condition could potentially result from meibomian gland atrophy.[19]

Study Visit

Contact lens wearers were asked to discontinue their CL use on the day of the study visit to avoid any tear film alterations that might result from CL removal.[20] All subjects were asked to not wear makeup and to refrain from using artificial tears on the day of the study visit to help avoid external bias. All subjects were required to complete their respective institution's consent and HIPAA (Health Insurance Portability and Accountability Act) forms before starting their study visit. Clinical tests were performed from the least to most invasive tests as seen in Table 1 to ensure minimal effects on subsequent assessments.[27] All relevant ocular, systemic, and CL history information was gathered via a questionnaire developed by the investigative team. All subjects were then asked to complete the Ocular Surface Disease Index (OSDI) questionnaire.[21,22]

Clinical measurements were obtained from both eyes. When data were collected from the upper and lower eyelids for a single test, the means of these values were used unless otherwise noted, based on past findings.[10] The first eye to be tested was randomly selected for osmolarity and Schirmer test I because the investigators hypothesized that fellow eyes may influence each other during these measurements.

A corneal topographer (E300 Corneal Topographer, Medmont) was used to determine noninvasive breakup time by recording the number of seconds required for the first distortion to appear on the reflected Placido disc rings.[20] Subjects were asked to repeat the procedure twice, and the mean of the three values was used in analysis. A multifunctional topographer (Keratograph 5M, Oculus, Inc) was used to measure tear meniscus height (TMH) as well as bulbar and limbal redness. Tear meniscus heights were measured by taking a single image of each eye, and the topographer's proprietary software was used to measure the subject's TMH in triplicate. A single image of bulbar and limbal redness was also taken, and these measurements were automatically calculated by the topographer's proprietary software.

Tear osmolarity was then obtained with a tear osmometer (TearLab Osmolarity System, TearLab Corporation). Tears were collected from the lower, lateral tear meniscus of each eye until the instrument sounded to indicate a sufficient sample (~50 nL, based on the instrument literature); the osmometer was then docked and allowed to calculate tear osmolarity, and these values were directly used in analysis.

A general slit-lamp examination with a biomicroscope was performed next. Upper and lower eyelid blepharitis was graded with Brubaker's 0 to 4 scale (Brubaker, KE. Provisional Patent No. 61/427,962, 2010). Eyelid margin erythema was analyzed in a similar manner; however, it was graded with a 0 to 3 scale.[23] The biomicroscope was then used to evaluate lid parallel conjunctival folds (LIPCOF) while the subjects were looking in primary gaze. The bulbar conjunctiva near the lower eyelid just below the temporal limbus was evaluated and graded according to Sickenberger et al.'s[24] grading scale (0 to 3). Meibomian gland expressibility (1 to 4 scale) and meibum quality (0 to 3 scale) were next assessed by first slightly everting the upper and lower eyelids, and they were graded with their respective scales.[25]

Corneal staining was evaluated with sodium fluorescein and a cobalt blue filter, and staining was graded according to the Cornea

TABLE 1.

Summary statistics for procedures completed during ocular surface assessment (worst eye)

Procedure	CL wearers, mean ± SD	NCL wearers, mean ± SD	Difference (p)
OSDI (0–100 scale)[21,22]	9.2 ± 11.5	7.8 ± 12.2	0.72
TBUT, s[20]	11.3 ± 6.6	9.5 ± 5.5	0.08
TMH, mm	0.3 ± 0.1	0.2 ± 0.1	0.11
Bulbar redness, U	0.8 ± 0.4	0.8 ± 0.3	0.80
Limbal redness, U	0.5 ± 0.3	0.5 ± 0.3	0.20
Tear osmolarity, mOsm/L	301.5 ± 10.7	304.2 ± 13.4	0.13
Blepharitis (0–4 scale)	0.6 ± 0.7	0.5 ± 0.7	0.54
Eyelid margin erythema (0–3 scale)[23]	0.4 ± 0.6	0.5 ± 0.6	**0.04**
Lid parallel conjunctival folds (0–3 scale)[24]	1.3 ± 0.9	1.0 ± 0.8	0.06
Meibomian gland expressibility (0–3 scale)[25]	2.1 ± 1.7	1.9 ± 1.7	0.66
Meibum quality (0–3 scale)[25]	0.9 ± 1.2	0.8 ± 1.2	0.88
Area of sodium fluorescein corneal staining (0–20 scale)[26]	1.2 ± 1.4	0.7 ± 1.1	**0.005**
Lissamine green conjunctival staining (0–20 scale)[27]	4.2 ± 3.9	2.6 ± 2.7	**0.006**
Lid wiper epitheliopathy (0–3 scale)[28]	0.6 ± 0.8	0.6 ± 0.7	0.60
Line of Marx (0–3 scale)[29]	0.6 ± 0.5	0.8 ± 0.7	**0.02**
Palpebral conjunctival hyperemia (1–4 scale)[26]	1.4 ± 0.5	1.4 ± 0.6	0.86
Lid roughness (1–4 scale)[26]	1.3 ± 0.4	1.4 ± 0.5	0.84
Meibomian gland dropout percentage (0–100%)[5]	24.0 ± 10.6	22.6 ± 12.9	0.34
Meiboscore (0–3 scale)[7]	2.6 ± 0.6	2.4 ± 0.6	0.06
Schirmer test I, mm	22.7 ± 10.9	22.5 ± 11.1	0.92

Worst eye was chosen by selecting the eye with the greatest amount of meibomian gland atrophy. Values are significant when p is less than 0.05. Significant p values are in boldface.

and Contact Lens Research Unit (CCLRU) grading scale (type, area, and depth) after 2.0 to 2.5 minutes.[26] The sum of the five area scores was used in analysis. Lid wiper epitheliopathy was evaluated with the previously instilled sodium fluorescein, and it was graded with Korb et al.'s[28] grading scale (length and width).

Conjunctival staining was evaluated with lissamine green and white light, and staining was assessed after about 2 minutes with the Oxford grading scale (0 to 5 scale) in four different quadrants (nasal, temporal, superior, and inferior).[27] The sum of these four area scores was used in analysis. Lid wiper epitheliopathy was evaluated with lissamine green, and it was graded with Korb et al.'s[28] grading scale (length and width). The mean of the length and width was calculated for both stains, and the mean of the lid wiper epitheliopathy values from both the sodium fluorescein and lissamine green evaluations was used in analysis.[28] The line of Marx was also evaluated at this time by everting the eyelids, using the previously instilled lissamine green and viewing the regions of interest with white light,[29] and graded with a 0 to 3 scale.[30] Palpebral conjunctival hyperemia and eyelid roughness were assessed by everting the eyelids again and viewing them with white light; they were graded using their corresponding CCLRU grading scales.[26]

Meibography images were collected with the multifunctional topographer.[5] Each subject's upper and lower eyelids were everted with a cotton-tipped applicator while the subject was seated in front of the topographer. Images of the upper and lower eyelids were successively collected until high-quality gland images were obtained. These images were next sent to the University of Waterloo where a single masked examiner determined both percent meibomian gland atrophy and meiboscore on two different days that were weeks apart. The area of percent atrophy was determined with ImageJ software, which can be obtained from the National Institutes of Health (http://imagej.nih.gov/ij/download.html), by outlining the meibomian gland area lost with the software's free hand selection tool (Fig. 1); this area was compared with the total meibomian gland region to determine the overall percentage of gland loss (0 to 100%).[5] Meiboscore was visually evaluated with Arita et al.'s[7] 0 to 3 grading. The eye with the worst percentage of gland loss was selected as the "worst eye," and the measurements from this eye were used in analysis for all statistical testing. If there was a tie between eyes, the right eye was selected for analysis.

Lastly, Schirmer test I (without anesthesia) was performed under habitual conditions to determine the amount of tears present.

Statistical Analysis

Surveys were administered via a secured web service (www.qualtrics.com), and all other data were collected with paper forms, which were later entered by the collecting investigator into a Research Electronic Data Capture software system. All data were analyzed using SAS 9.3. Descriptive statistics such as means and SDs were used to describe the data. The association between CL wear and meibomian gland atrophy was the question of interest. Paired *t* tests were used to determine differences between groups for the clinical signs and symptoms. Conditional logistic regression is an analytic technique used to account for the correlation introduced into the study design when pair matching is used.[31] Because this was a matched-pair study on CL wear, the conditional logistic regression was used to account for the matched-pair design and investigate associations between meibomian gland atrophy, CL wear, clinical signs, and OSDI symptom scores. After comparing univariate models for the clinical signs, atrophy, and CL wear, multivariate models including these variables and atrophy together were built. Multivariate model fit was assessed using the -2 log likelihood statistic to determine the covariates that added significantly

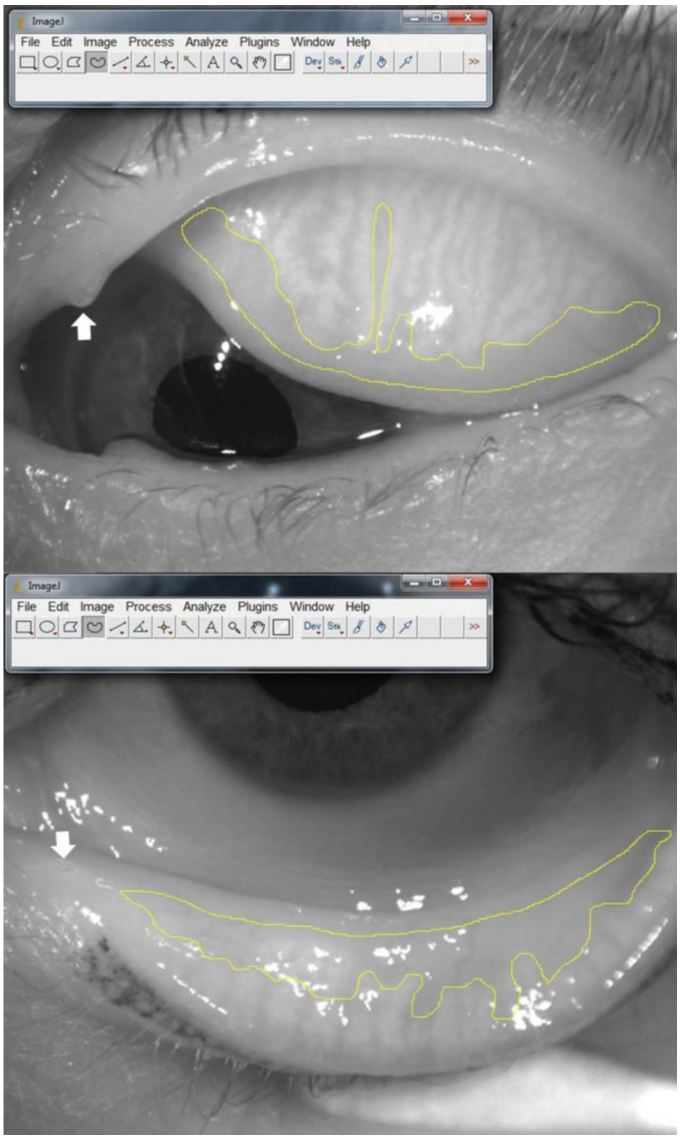

FIGURE 1.

Meibography image analysis examples. The freehand tool in ImageJ was used to select the area of meibomian gland atrophy in the everted superior eyelid (top) and the everted inferior eyelid (bottom). Area loss is expressed as a percentage of the total area of the palpebral surface. The arrowheads mark the punctum. A color version of this figure is available online at www.optvissci.com.

to the model. Variables were added in a stepwise fashion to determine the impact on the model. When the −2 log likelihood statistic indicated no additional improvement with the addition of further variables to the model, model building was complete. The resulting OR details the association between the model variables and the likelihood of being a CL wearer. For example, an OR greater than 1 indicates that the covariate of interest is more likely to occur in a CL wearer.

RESULTS

A total of 142 adult subjects (71 matched pairs) were recruited across the five different sites. One of the 71 matched pairs was excluded from analysis because of missing data; therefore, all calculations are based on 140 subjects. The sample was 63% female. The mean (±SD) age was 30.6 (±12.4) years and 30.1 (±12.2) years for CL wearers and NCL wearers, respectively. A total of 6.3% of the sample reported having dry eye and 3.5% of the sample reported having ocular allergies. Beyond the 1-year ocular surgery exclusion, there was one CL wearer who had a radial keratectomy 20 years ago and one NCL wearer who had LASIK (laser-assisted *in situ* keratomileusis) 15 years ago. The occurrence of the above conditions was inadequate to perform any subanalysis with study observations.

The mean (±SD) for each group for each parameter tested can be found in Table 1. The only significant differences between the CL and NCL wearers were eyelid margin erythema ($p = 0.04$), total area of lissamine green staining ($p = 0.006$), a more anteriorly displaced line of Marx ($p = 0.02$), and total area of corneal sodium fluorescein staining ($p = 0.005$). The only clinically significant differences were with the lissamine green and sodium fluorescein staining results. A clinically significant difference was found when a difference between groups was greater than the smallest grading increment used in our scales. In general, a clinically significant difference between groups was one unit on a grading scale, with the exception of sodium fluorescein staining, which was a half-unit difference between groups. A subanalysis of corneal sodium fluorescein (type, area, and depth) and lissamine green staining by region of staining is reported for the two groups in Tables 2 and 3, respectively. The CL group had significantly greater sodium fluorescein staining for the inferior area (0.04) and for the temporal area (0.01) (Table 2) and significantly greater lissamine green staining for the inferior area ($p = 0.001$) and the temporal area ($p = 0.03$) (Table 3). Nevertheless, none of these regional differences were large enough to be clinically significant.

As indicated in METHODS, the associations given by the conditional logistic regression analysis between meiboscore and CL status speak to the likelihood of occurrence relative to CL wear. It was determined that there was a nonsignificant, 70% increase in the odds of being a CL wearer for each increase in grade of meiboscore in the CL group compared with the NCL group (OR, 1.7; 95% confidence interval [CI], 0.97 to 2.98; $p = 0.06$), which is a nonsignificant positive association between the presence of atrophy and CL wear. After controlling for the significant relation between CL wear and eyelid margin erythema ($p = 0.01$), LIPCOF ($p = 0.04$), total area of lissamine green conjunctival staining (0.04), or lid wiper epitheliopathy ($p = 0.04$), there was a positive association between a higher meiboscore and being a CL wearer (Table 4); with the exception of eyelid margin erythema, all of these variables showed an increased odds of occurrence in the CL wearers compared with NCL wearers (OR, >1.8). All other variables were not significantly related to CL wear when considered with meiboscore in this regression model: OSDI ($p = 0.06$), tear breakup time (TBUT) ($p = 0.06$), TMH ($p = 0.06$), bulbar redness ($p = 0.07$), limbal redness ($p = 0.08$), tear osmolarity ($p = 0.06$), blepharitis ($p = 0.07$), meibomian gland expressibility ($p = 0.06$), meibum quality ($p = 0.06$), total area of sodium fluorescein corneal staining ($p = 0.09$), line of Marx ($p = 0.07$), palpebral conjunctival hyperemia ($p = 0.06$), eyelid roughness ($p = 0.06$), and Schirmer test (0.06). Additional model building using meiboscore with the other significant variables was performed. The best-fit multivariable logistic regression model showed that the odds of being a CL wearer increased

TABLE 2.
Sodium fluorescein corneal staining assessment with the CCLRU grading scale[26]

Grading scale	CL wear, mean ± SD	NCL wear, mean ± SD	Difference (p)
Staining type (0–4 scale)			
Central	0.2 ± 0.5	0.3 ± 1.1	0.37
Temporal	0.5 ± 1.1	0.3 ± 1.0	0.15
Inferior	0.8 ± 1.3	0.6 ± 1.2	0.19
Superior	0.5 ± 1.4	0.2 ± 0.6	0.14
Nasal	0.5 ± 1.0	0.4 ± 1.1	0.35
Staining area (0–4 scale)			
Central	0.1 ± 0.3	0.1 ± 0.2	0.48
Temporal	0.2 ± 0.5	0.1 ± 0.3	**0.01**
Inferior	0.4 ± 0.7	0.3 ± 0.6	**0.04**
Superior	0.2 ± 0.4	0.1 ± 0.3	0.40
Nasal	0.3 ± 0.4	0.2 ± 0.4	0.08
Total	1.2 ± 1.4	0.7 ± 1.1	**0.001**
Staining depth (0–4 scale)			
Central	0.1 ± 0.3	0.1 ± 0.4	0.80
Temporal	0.2 ± 0.5	0.1 ± 0.4	0.20
Inferior	0.4 ± 0.5	0.3 ± 0.5	0.16
Superior	0.2 ± 0.5	0.1 ± 0.4	0.36
Nasal	0.3 ± 0.5	0.2 ± 0.4	0.08

Type: 1, micropunctate; 2, macropunctate; 3, coalescent macropunctate; 4, patches. Area: 1, 1–15%; 2, 16–30%; 3, 31–45%; 4, greater than 45%. Depth: 1, superficial epithelium; 2, deep epithelium; 3, immediate localized stromal glow; 4, immediate diffuse stromal glow. Values are significant when p is less than 0.05. Significant p values are in boldface.

145% (OR, 2.45, 1.27, and 4.73) with every unit increase in meiboscore; that is, the higher the meiboscore, the more likely the subject was a CL wearer, when controlling for the relationship that conjunctival staining (OR, 1.25; 95% CI, 1.07 to 1.45) and lid margin erythema (OR, 0.25; 95% CI, 0.09 to 0.71) have with CL wear in the presence of atrophy. Conditional logistic regression with percent meibomian gland atrophy and CL status was unable to find any significant associations even after controlling for the other variables.

DISCUSSION

Obata[32] defined gland atrophy as "a diminished volume of cells under certain pathologic conditions after normal development of cells and tissue." This manifests in meibomian gland atrophy with acinar tissue dedifferentiation and decreased meibum volume.[1] Whereas Arita et al. have previously suggested that CL use was involved in the mechanism leading to meibomian gland atrophy,[6] the current study was unable to find strong evidence to support this claim. When directly comparing CL and NCL wearers, we found a nonsignificant difference in atrophy between the two groups (Table 1). Furthermore, we were unable to find associations between CL use and percent meibomian gland atrophy in regression analysis, yet we were able to find associations between CL use and meiboscore in similar analyses. In fact, a best-fit multivariate regression model with meiboscores indicated that there was an increase in the odds that a subject was a CL wearer with each increase in meiboscore grade. Specifically, with every unit increase in meiboscore, the odds of a subject being a CL wearer increased by 2.45 (odds increase of 145%), when controlling for conjunctival staining and eyelid margin erythema. This study also indicated that LIPCOF and lid wiper epitheliopathy might be linked to CL-related meibomian gland atrophy. These associations may indicate that CLs could produce these negative effects on meibomian glands through mechanical interaction with the eyelids,[6] by altering the natural blink,[33] or through some other potential mechanism yet to be discovered. Although these regression analysis results are interesting, they show that if there is an association, it is likely not a straightforward one. These unclear results may only be resolved with a longitudinal study that evaluates CL-related meibomian gland atrophy or with animal studies that are aimed at understanding the mechanism of meibomian gland atrophy development.

As alluded to above, a potential association between meibomian gland atrophy and CL use is corroborated by Arita et al.'s cross-sectional study,[6] which analyzed 121 CL wearers and 137 NCL wearers. Overall, Arita et al.[6] determined that meiboscores were significantly greater in the CL wearers than the NCL wearers; they also found that meiboscores significantly increased with years of CL use. Arita et al.[6] also failed to find a correlation between meibomian gland atrophy (in the presence of CL use) and overall eyelid abnormality, TBUT, corneal sodium fluorescein staining,

TABLE 3.
Lissamine green conjunctival staining assessment with the Oxford grading system[27]

Staining area	CL wear, mean ± SD	NCL wear, mean ± SD	Difference (p)
Inferior conjunctiva	0.5 ± 1.1	0.1 ± 0.3	0.001
Nasal conjunctiva	1.9 ± 1.8	1.4 ± 1.6	0.10
Superior conjunctiva	0.4 ± 0.9	0.2 ± 0.7	0.15
Temporal conjunctiva	1.2 ± 1.4	0.8 ± 1.2	**0.03**

Values are significant when p is less than 0.05. Significant p values are in boldface.

TABLE 4.
Different multivariate conditional logistic regression models assessed that describe significant meiboscore relationships

Procedure	OR (95% CI)	p
Model 1*		
Eyelid margin erythema (0–3 scale)[23]	0.30 (0.12–0.76)	**0.01**
Meiboscore (0–3 scale)[7]	2.12 (1.16–3.87)	**0.01**
Model 2		
Lid parallel conjunctival folds (0–3 scale)[24]	1.66 (1.02–2.70)	0.43
Meiboscore (0–3 scale)[7]	1.83 (1.02–3.30)	**0.04**
Model 3		
Lissamine green conjunctival staining (0–20 scale)[27]	1.22 (1.07–1.40)	**0.004**
Meiboscore (0–3 scale)[7]	1.88 (1.03–3.41)	**0.04**
Model 4		
Lid wiper epitheliopathy (0–3 scale)[28]	1.35 (0.77–2.37)	0.30
Meiboscore (0–3 scale)[7]	1.84 (1.02–3.30)	**0.04**

Significant p values are in boldface.
*Multivariate models with significant covariates ($p \leq 0.05$).

and Schirmer test, which was also the case in the present study. To the best of our knowledge, the work of Arita et al.[6] and ours are the only studies performed thus far to specifically analyze CL-related meibomian gland atrophy associations. Nevertheless, others have analyzed other aspects of meibomian gland atrophy.[5,7–10,12,13,34]

The current study design also allowed us to determine if signs and symptoms were different between CL wearers and NCL wearers. Specifically, our analysis found that eyelid margin erythema, corneal sodium fluorescein staining, conjunctival lissamine green staining, and line of Marx were significantly different between the two groups (Table 1). Although our study is not the first to analyze this topic, to the best of our knowledge, our study is the most comprehensive analysis to date. Although most of the results from the present study agree with past studies on this topic,[13,35–38] there were some disagreements.[13,35,36] For example, Villani et al.'s study[13] found TBUT and gland expressibility to be different between the two groups whereas the present study did not find a difference. Differences in results may have arisen because Villani et al.[13] recruited symptomatic subjects whereas the present study mostly had normal subjects. An additional discrepancy was with Guillon and Maissa's work,[35] which determined that there was no significant difference in lissamine green staining between the two groups, and they found that the CL group was significantly more likely to have symptoms than the NCL group. These differences may have arisen because Guillon and Maissa[35] did not match on age or sex and because they used a different symptoms survey (McMonnies vs. OSDI) from the present study.

The above study design and data have provided new information about the effects of CL use and meibomian gland atrophy, yet our results, like any study, are not without limitations. One potential concern is that the original study was designed to find differences in atrophy between groups, not associations with atrophy. The sample size for the designed study was to compare meibomian gland atrophy between an unmatched case-control sample. Based on variability data from Arita et al.[7] and an effect size of 0.55 from their data, the sample size was 71 subjects per group. The sample size calculated for this study was not directed at answering questions about associations with atrophy. As such, it is more appropriate to present the power for the comparison we evaluated in this analysis. Because of the matched case-control design of the study, and the desire to look at the factors associated with CL wear, a power analysis specific to this type of analysis was conducted using PASS (NCSS, Kaysville, UT). Input parameters into this calculation were the number of case patients, the number of control subjects, an estimate of the probability of exposure of a poor meiboscore in the NCL wearers, and an estimate of phi (correlation between case patients and control subjects for meiboscore). Using the results from the best-fit model, we have 60% power to detect an OR of 2.45. Because the difference between the two groups was smaller than anticipated, this result is not surprising.

Matching on the exposure of interest may also be a limitation, resulting in the reported OR being an underestimate of the association between CL wear and atrophy.[39] This would occur if there were too much variance removed from the analysis by the matching on CL wear. Another limitation is related to the fact that the case-control study can only indicate associations between variables. Causality, like temporality, is not able to be determined, in these studies. Nevertheless, matching on age and sex was deemed to be an important step in the study design because this allowed us to control for two factors that may be strongly related to meibomian gland atrophy.

The exclusion of overnight CL wearers and CL dropouts has also limited the generalizability of our study because of the exclusion of subjects who may potentially be at the highest risk for meibomian gland atrophy. Only including successful CL wearers may also mean that we may have introduced a survivor basis into our data set, which could have decreased the effect size seen between groups. Nevertheless, the authors felt that these were important exclusion factors to limit the sources of variations between pairs. These issues could potentially be addressed in a future study that is designed to address meibomian gland atrophy in all types of CL wearers over a multiple-year period.

In conclusion, the information obtained from this study not only adds to our understanding of how CLs affect the eye but also allows us to advise practitioners about the relatively few ocular surface changes that may result from habitually wearing CLs. Likewise, this study found an inconclusive association between CL use and meibomian gland atrophy that supports the need for a

longitudinal, prospective evaluation of meibomian gland atrophy in CL wearers to determine if there is a true association between CL use and meibomian gland atrophy.

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