Tear Film, Contact Lens, and Patient-Related Factors Associated with Contact Lens–Related Dry Eye

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Purpose. To examine tear film, contact lens, medical, and patient-related factors associated with self-reported contact lens–related dry eye.

Methods. Four hundred fifteen contact lens wearers were recruited and enrolled in this phase of a larger cross-sectional study. A variety of tear film (e.g., interferometry, osmolality, phenol red thread, meibography, fluorescein, and lissamine green staining), contact lens (i.e., water content, refractive index, material), and patient-related (e.g., gender, sociodemographic, education, income, and medical health) factors were examined in relation to dry eye status. Univariate and multivariate logistic regression models were used to examine the relation between these tear film, contact lens, and patient-related factors associated with dry eye status.

Results. Of the 415 enrolled, the data from 360 were used in the analyses. The average age was 31.1 ± 11.5 years, 245 (68%) participants were female, and 55.3% were classified as having–contact lens–related dry eye via self-report. Overall, 327 (90.8%) were hydrogel lens wearers and 33 (9.2%) were gas-permeable lens wearers. Several factors were shown to be related to dry eye status in multivariate modeling, including female gender ($P = 0.007$), lenses with higher nominal water content ($P = 0.002$), rapid prelens tear film thinning time ($P = 0.008$), frequent usage of over-the-counter pain medication ($P = 0.02$), limbal injection ($P = 0.03$), and increased tear film osmolality ($P = 0.05$).

Conclusions. Contact lens–related dry eye may be explained mechanistically by increased tear film thinning times (evaporation or dewetting) resulting in increased tear film osmolality. Other contributing factors include the use of high-water-content lenses, which have traditionally been reported to be associated with less patient comfort than lower-water-content lenses, potentially due to spoilation and deposition. As found in other studies of dry eye, women are more likely to report contact lens–related dry eye than are men. (*Invest Ophthalmol Vis Sci.* 2006;47:1319–1328) DOI:10.1167/iovs.05-1392

Dry eye syndrome has typically been characterized in recent epidemiologic studies by self-reported symptoms, and these studies indicate that dry eye disease is prevalent in 0.39% to 33.7% of the general population.[1–8] We recently found that approximately 50% of contact lens wearers report experiencing dry eye symptoms at least occasionally, which is in good agreement with several other reports on the frequency of contact lens–related dry eye.[1,9–13] We also showed that contact lens wearers are 12 times more likely than clinical emmetropes and five times more likely than spectacle wearers to report dry eye.[14] In the United States, there are approximately 35 million contact lens wearers, which suggests that as many as 17 million contact lens wearers experience significant dry eye symptoms.[15] Dry eye and alterations of the tear film in contact lens wearers are associated with reductions in functional visual acuity,[16,17] reductions in wearing time,[18] and an increased risk of ocular surface desiccation, bacterial binding, and infection.[19,20] The primary reasons for contact lens intolerance and discontinuation are discomfort and dryness.[21,22]

Because dry eye symptoms affect the wearing prognosis of contact lens wearers, it is important to understand factors that are associated with patient-reported symptoms. Tear film, contact lens, medical, sociodemographic, and other factors associated with these symptoms are not understood. It has been speculated that potential mechanisms of contact lens–related dry eye include increased evaporation of the tear film,[23] inflammation,[24–26] reduced ability to produce adequate tears with concurrent increased osmolality,[27,28] dewetting related to lack of biocompatibility of the lens surface,[29–33] or any combination of these. Yet, the true etiology of contact lens–related dry eye remains elusive.

The purpose of this study was to examine tear film, contact lens, and other patient-reported factors associated with contact lens–related dry eye. It was hypothesized that contact lens wear leads to changes in structure or production of the meibomian glands, which leads to alterations in the lipid layer thickness and tear film instability, an increase in tear film osmolality, and dehydration of hydrogel lenses. This process, in turn, leads to the commonly reported symptoms of dryness in contact lens wearers. The purpose of this study was to test these, in addition to other tear film-related, medical, and sociodemographic factors associated with self-reported dry eye in contact lens wearers.

Materials and Methods

Study Design, Patient Sample, and Dry Eye Classification

This research was approved by the Biomedical Institutional Review Board, in accordance with the tenets of the Declaration of Helsinki. The study (The Contact Lens and Dry Eye Study [CLADES]) was a two-phase, cross-sectional survey with a nested case–control design. The purpose of phase I (the cross-sectional survey) was to determine the distribution of contact lens–related dry eye, and to serve as a screening and recruiting vehicle for phase II (the nested case-control/examination phase). For phase I, individuals from a large, university-based ophthalmic clinic and the surrounding community were surveyed with the Contact Lens Dry Eye Questionnaire (CLDEQ),[9] results of which have been described.[14,34] Clinic-based patients completing the questionnaire were those presenting only for routine ophthalmic care. Patients presenting to the clinic for follow-up or problem-based care were not eligible to complete the questionnaire. During the survey, patients were asked if they would like to return for an examination visit (phase II).

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The purpose of phase II (the examination) was to determine clinical and patient-related factors associated with contact lens–related dry eye. In addition, patients again completed the CLDEQ at this examination visit to ensure consistency in classification; in this regard, an average CLDEQ score was calculated, after which a previously described cutoff score was applied that classifies patients according to dry eye status.[9,34] Patients returning for the examination visit completed a variety of other clinical and questionnaire assessments described in the next section.

Data Collection and Outcome Measures

Data collection for cases and controls was performed in an identical manner, without examiner knowledge of dry eye status. Safeguards were used to protect against the clinician's becoming unmasked relative to disease status (i.e., the study coordinator performed scheduling, the ophthalmic history survey was self-administered by the patient at the completion of the examination). All clinical tests were performed on the right eye of the subject, with appropriate rest intervals associated with the more invasive tests that might induce tearing. The clinical outcome measures related to the hypothesis testing are detailed in the following text and are outlined in the order in which they were performed in the examination.

Prelens Lipid Layer Thickness and Tear Film Thinning Time. A thickness-dependent fringe (TDF)–imaging interferometer was used in this study to assess prelens tear film (PLTF) lipid layer thickness, wherein the wavelength and angle are the same but the thickness varies.[35,36] Using this method, black and white responses are associated with thin films (<120 nm), and orange, brown, blue, and yellow colors are associated with medium thicknesses (120–300 nm), which is related to the blue-yellow response of the visual system. As the lipid layer (a high-index thin film) is generally less than 100 nm, and the order (m) is less than 0.5, lighter regions from TDF images correspond to thicker regions of lipid. The patient is asked to blink normally while the examiner assigns a real-time tear (lipid layer) interference pattern classification.[36]

This same interferometer was next used to examine PLTF thinning time via noninvasive methods (i.e., without fluorescein). This method reduces any alteration of the tear film by the instillation of fluorescein and minimizes the potential for reflex tearing. When obtaining PLTF thinning times, patients are asked to hold both eyes open while the examiner times the interval from the last blink to the first break, dry spot, or distortion occurring in the tear pattern.[36–39] Patients were encouraged to blink if they felt discomfort, to avoid reflex tearing. If a patient blinked during the test sequence before tear film break-up, he or she was instructed to rest briefly to allow the tear film to stabilize, and the measure was repeated with reinforcement of the instructions. Three measures of PLTF thinning times were taken, and an average was used in statistical analyses. After this, a brief contact lens fit assessment was conducted by slit lamp biomicroscopy, followed by removal of the right lens and immediate measurement of water content and refractive index (for hydrogel lenses) as described below.

Contact Lens Material, Water Content, and Refractive Index. In addition to assessing material type (hydrogel versus gas permeable), water content and refractive index were also determined so that lens dehydration could be assessed (nominal water contents and refractive indices are reported by the manufacturers). An automatic refractometer (CLR 12-70; Index Instruments, Cambridge, UK) was used that is designed to measure not only the water content, but also the refractive index of hydrogel lenses.[40] After a contact lens fit assessment, the patient was instructed to remove his or her right contact lens and to place it immediately on the refractometer for assessment. The measured values were then compared to the nominally reported refractive index and water content for the specific lens material to determine dehydration of the lens. Refractive index increases as water content decreases; thus, as a lens dehydrates, its refractive index increases. Because silicone hydrogel lenses do not maintain a linear relation between water content and refractive index, water content measures of these lenses are not feasible with a refractometer. Thus, only the refractive index is obtained when a patient is wearing a silicone hydrogel lens.[40] For both refractive index and water content, change in hydration is determined as follows: nominal value minus measured value. While the examiner was conducting this measurement, the patient was asked to complete a sociodemographic survey regarding age, gender, race, economic, and educational status.

Osmolality. After completion of refractometry and the sociodemographic survey, a 200-nL tear sample was taken for analysis of osmolality using an osmometer (Advanced Instruments, Inc., Needham Heights, MA). The sample was taken from the meniscus of the right eye with a capillary tube. Caution was taken to avoid irritating the ocular surface, to reduce reflex tearing. The patient was then asked to complete two additional surveys after the tear sample was collected including the positive and negative affect survey (PANAS)[41] and a health behavior–related survey that allowed a rest period of approximately 10 minutes.

Slit Lamp Biomicroscopy. After the patient completed the two aforementioned surveys, slit lamp biomicroscopy of the anterior segment (lids, cornea, and conjunctiva) was conducted. During this examination, the vertical dimension associated with the tear meniscus (i.e., height in millimeters) was measured with a reticule calibrated for 16× magnification.[42] Bulbar and limbal hyperemia, lid margins (capping and telangiectasia), and tear film debris were graded on clinically accepted scales of grade 1 (none) to grade 4 (severe). A blink evaluation was completed according to the following grading scale: (1) complete blink (involuntary complete blink), (2) incomplete blink (descending upper lid covers less than two thirds of the cornea), (3) forced blink (complete voluntary blink; lower lid raised producing a near squint), and (4) twitch blink (almost undetectably small movement of upper lid).[43]

Phenol Red Thread Test. After the slit lamp biomicroscopy examination, tear production rates and/or tear volume were determined with the phenol red thread test (Zone Quick; Menicon, Nagoya, Japan).[44,45] Briefly, the thread was inserted over the inferior lid margin toward the temporal canthus, and the patient was instructed to look straight ahead for 15 seconds, blinking normally. After this time, the thread was removed and measured to the nearest millimeter.

Meibography. Patients underwent digital video meibography imaging, in which transillumination of the right lower eyelid was conducted with a transilluminator and fiber-optic light guide with near-infrared (IR) light (650–700 nm), as previously described.[46] Central images from the right lower eyelid were recorded with a near-IR, one-chip, charge-coupled device camera (model KP-M2R; Hitachi, Tokyo, Japan). The camera was mounted on a slit lamp and hooked directly to a computer for video capture, and each sequence was 1200 frames in length (at 30 frames/s). All images were captured from the central eyelid at 10× slit lamp magnification. Grading scales and the reliability of our method have been reported.[46] Briefly, they include counting of glands in addition to a categorical gestalt scale associated with overall gland loss. All images were graded by a masked reader, who graded each image on two occasions separated by at least 7 days. When there were discrepancies associated with the two readings for the gestalt (categorical) scale made by the first masked reader, a second masked reader adjudicated the grade by performing an independent assessment of the image. For gland counting, an average of the two readings performed by the first examiner was used in the statistical analyses.

Corneal and Conjunctival Staining. Staining of the ocular surface was recorded for five areas of the cornea, as proposed in the Report of the National Eye Institute and Industry-Sponsored Dry Eye Workshop.[23] A 5-μL sample of 2% liquid fluorescein was applied to the bulbar conjunctiva with a micropipette (Finipipette; Thermo Lab-Systems, Franklin, MA). After instillation, a barrier filter (Wratten no. 12; Eastman Kodak, Rochester, NY) was used to enhance contrast when assessing staining of the cornea. The extent of the corneal surface area stained was graded for each of the five locations, and a

TABLE 1. Sample Size Estimates Associated with the Outcomes of Interest as They Related to Contact Lens–Related Dry Eye

Risk Factor	Criteria	Frequency or Mean for Control Group*	Odds Ratio or % Difference	Number Per Group	Total Sample Size†
PLTF thinning time	20% Reduction	13.0 ± 7.6 sec	20%	137	317
Meibomian gland disease	Gestalt grade ≥3	19.6%	2.25	136	315
	Gland Count: <7	41.7%	2.25	107	248
Contact lens dehydration	40% Reduction	−3.4% ± 3.5%	40%	136	329
High water, hydrogel lens wear	>50% Nominal water content	68.9%	2.25	150	347

* Estimates from the scientific literature or pilot studies conducted in planning the present study.
† Increased by ~15% for a margin of error correction (i.e., missing data).

total surface-area staining score was generated (20 possible points). A version of the Cornea and Contact Lens Research Unit (CCLRU) grading scales was used for surface area grading as follows: grade 0: none; grade 1: 1% to 15% surface area; grade 2: 16% to 30%; grade 3: 31% to 45%; and grade 4: more than 45%.

Immediately after assessment of corneal fluorescein staining, 10 μL of a 1% liquid solution of lissamine green was applied to the bulbar conjunctiva also using a micropipette (Finipipette; Thermo LabSystems). After instillation, conjunctival staining was graded in each of the six areas diagrammed schematically in the aforementioned Report of the National Eye Institute and Industry-Sponsored Dry Eye Workshop but using the surface area grading scheme associated with the Oxford grading scale.[23,47] After ocular surface staining assessments, patients were asked to complete a general medical history form and an ophthalmic history form, both of which related to systemic and ocular comorbidities, and the patient examination was completed.

Sample Size and Statistical Analyses

All statistical analyses were performed with Statistical Analysis Software (SAS, ver. 9.1; SAS Institute, Carey, NC).

Sample Size. Sample size was determined a priori based on statistical methods for comparisons of means and proportions, and Table 1 shows sample size estimates for phase II of the study relative to the main outcomes of interest. All sample size estimates in the table were inflated by at least 15% for margin of error correction (e.g., sampling errors, missing data). These sample size calculations also assume a one-to-one sampling ratio of dry eye cases to controls. The outcome associated with the largest sample size is high-water-content contact lens wear, which shows that in total at least 347 cases and controls would be needed to detect a clinically significant increase in the odds (OR = 2.25) of contact lens–related dry eye if it were associated. Thus, the total sample size needed for the case–control phase (phase II) of the study is driven by the assessment of high-water-content lens wear, which should allow for the detection of clinically relevant differences in the other factors proposed as being associated with contact lens–related dry eye.

Hypothesis Testing. Descriptive statistics were used to compare the distributions of study variables in those with and without dry eye (the dichotomous outcome). For continuous variables, means were used to characterize central tendency, and standard deviations were used to characterize dispersion. For categorical variables, contingency tables were used to characterize the distribution of variable values.

Logistic regression was used to model the relation between self-reported dry eye disease and independent variables (predictors). The process of building a multivariate model began with a univariate analysis of each possible predictor. For continuous and categorical patient-related and ophthalmic data, univariate logistic regression models were produced to describe the relationship between each predictor variable and the outcome (dry eye [DE] or no dry eye [NDE]). For general dichotomous health information, the Fisher exact test was used to assess the relationship between dry eye disease and each variable. On completion of the univariate analyses, an initial multivariate logistic regression analysis was fit, with all variables associated with dry eye disease in the univariate tests at the $\alpha \leq 0.25$ level included. The initial multivariate model was the result of a stepwise procedure, with entry and exit criteria set at $\alpha \leq 0.25$. A second stepwise multivariate model was fitted with the variables selected by the first stepwise procedure. The second stepwise procedure used a more strict criterion of $\alpha \leq 0.10$ for inclusion, after which selected variables and their interactions were examined in a new model with selection criterion set at $\alpha \leq 0.05$. This concluded the model-building steps and led to a final model that best predicted self-reported dry eye status, given the data collected. Odds ratios (ORs), 95% confidence intervals (CIs), and probabilities of the model parameter estimates are reported for the final models.

The Hosmer-Lemeshow goodness-of-fit test was used to examine the calibration of the multivariate model.[48] When the χ^2 result for this test is small (larger probability), the model is considered well calibrated (i.e., the model appears to provide accurate estimates of the probability of predicting dry eye status based on the independent variables). The discriminative ability of the model was evaluated using the area under the receiver operating characteristic (ROC) curve (i.e., can the model accurately discriminate between those who self-report dry eye disease and those who do not?). Discrimination was assessed according to the following guidelines for area under the ROC curves: 0.5, no discrimination; between 0.7 and 0.8, acceptable discrimination; between 0.8 and 0.9, excellent discrimination; and greater than 0.9, outstanding discrimination.[48]

RESULTS

Patient Sample

Four hundred fifteen patients were enrolled in this phase of the study, although 360 patients were included in the sample reported here, because 55 had missing CLDEQ survey classification data. The average age of patients in the sample was 31.1 ± 11.5 years and 245 (68%) were women. Overall, 327 (90.8%) were hydrogel lens wearers and 33 (9.2%) were gas-permeable lens wearers, with an overall average length of wear of 8.6 ± 6.4 years. There were 199 (55.3%) classified with dry eye by self-report on the CLDEQ and 161 (44.7%) participants classified without dry eye by self-report.

Univariate Analyses

Table 2 displays means and standard deviations of continuous predictor variables stratified by dry eye status, in addition to results for univariate logistic regression analyses for each variable. PLTF thinning time was most strongly associated with dry eye status ($P = 0.0006$). The average PLTF thinning time for the DE group was 8.23 ± 5.67 seconds and 11.03 ± 8.63 seconds for the NDE group. The PLTF thinning time was followed by nominal water content ($P = 0.003$). The average in the DE group was 53.09% ± 13.20% and in the NDE group was 47.90% ± 15.21%. Similar to nominal water content, nominal refractive index was also related to dry eye status ($P = 0.004$). The average in the DE group was 1.408 ± 0.017 and in the NDE group was 1.413 ± 0.016. Osmolality was also signifi-

TABLE 2. Univariate Logistic Regression Analyses of "Continuous" Predictor Variables of Factors Associated with Contact Lens–Related Dry Eye

Outcome	Dry Eye Mean ± SD (*n*)	Non–Dry Eye Mean ± SD (*n*)	Odds Ratio	95% CI	*P*
PLTF thinning time (sec)	8.23 ± 5.67 (199)	11.03 ± 8.63 (161)	0.94	0.91 to 0.98	0.0006
Nominal water content (%)	53.09 ± 13.20 (160)	47.90 ± 15.21 (128)	1.03	1.01 to 1.04	0.003
Nominal refractive index	1.408 ± 0.017 (160)	1.413 ± 0.016 (128)	0.81	0.70 to 0.94	0.004
Osmolality (mOsM)	307.66 ± 32.39 (174)	297.06 ± 31.82 (139)	1.01	1.01 to 1.02	0.005
Measured refractive index	1.428 ± 0.016 (164)	1.432 ± 0.013 (143)	0.81	0.70 to 0.95	0.009
Negative affect	19.57 ± 5.88 (199)	18.19 ± 5.64 (161)	1.04	1.01 to 1.08	0.02
Measured water content (%)	52.09 ± 7.52 (175)	50.30 ± 6.72 (146)	1.04	1.00 to 1.07	0.03
Phenol red thread (mm)	19.26 ± 7.09 (199)	20.50 ± 6.52 (161)	0.97	0.94 to 1.00	0.09
ΔRefractive index*	0.019 ± 0.008 (147)	0.018 ± 0.008 (125)	1.18	0.86 to 1.61	0.30
Tear meniscus height (mm)	0.22 ± 0.11 (198)	0.24 ± 0.10 (160)	0.26	0.03 to 1.93	0.19
Fluorescein staining (extent)	1.71 ± 2.87 (198)	2.16 ± 3.91 (161)	0.96	0.90 to 1.02	0.22
Fluorescein staining (depth)	1.24 ± 1.62 (199)	1.35 ± 1.90 (161)	0.96	0.85 to 1.09	0.55
ΔWater content*	−4.34 ± 3.38 (135)	−4.17 ± 3.21 (95)	0.98	0.91 to 1.07	0.70
Age (y)	31.00 ± 10.83 (199)	31.36 ± 12.43 (161)	1.00	0.98 to 1.02	0.76
Lissamine green staining (depth)	3.83 ± 3.13 (199)	3.76 ± 2.90 (161)	1.01	0.94 to 1.08	0.82
Lissamine green staining (extent)	5.20 ± 4.76 (199)	5.16 ± 4.93 (161)	1.00	0.96 to 1.05	0.95
Positive affect	34.89 ± 6.09 (199)	34.87 ± 6.07 (161)	1.00	0.97 to 1.04	0.97

The probability is associated with the Wald χ^2 test of the hypothesis that the parameter of the logistic regression model is zero.
* Measured − nominal.

cantly related to dry eye status ($P = 0.005$). The average in the DE group was 307.66 ± 32.39 mOsM and the average in the NDE group was 297.06 ± 31.82 mOsM. Finally, both measured refractive index status ($P = 0.009$) and measured water content ($P = 0.03$) were significantly related to dry eye, in that higher-water-content (lower refractive index) materials were related to dry eye status. Given the strong correlation between nominal water content and measured water content and nominal refractive index and measured refractive index, the measured values were removed from consideration in multivariate modeling, because their highly correlated nominal counterparts are more readily accessible.

Tables 3 and 4 display frequency estimates for categorical variables stratified by dry eye status. Gender was strongly associated with dry eye status ($P < 0.0001$); 40% of the men and 62% of the women were classified as having DE. The distribution of lipid layer thickness was also strongly associated with dry eye status ($P = 0.0014$). In this regard, those classified with dry eye were much more likely to have thinner lipid layers (either absent, open meshwork, or closed meshwork) than were those classified as NDE. As shown in Table 4 (which lists general health conditions and medication usage distributions), a history of seasonal allergies was significantly associated with dry eye (62.9% of those classified with dry eye versus 37.1% of those without dry eye, $P = 0.004$). No other patient-related, clinical, or medical factors were significantly associated with dry eye status in univariate analyses.

Multivariate Analyses

Again, the initial step in multivariate analyses was the inclusion of variables from univariate analyses that met the $\alpha \leq 0.25$ entry criteria. Eighteen variables from Tables 2, 3, and 4 were included in the initial step. After inclusion in a multivariate model, nine of the 18 variables were selected (at $\alpha \leq 0.25$), including gender, nominal water content, PLTF thinning time, osmolality, tear film debris, limbal injection, the use of over-the-counter pain medications at least three times per week, history of conjunctivitis, and history of seasonal allergies. These nine variables were then resubmitted for stepwise selection with the criterion tightened to $\alpha \leq 0.10$, and eight variables were selected including gender, nominal water content, PLTF thinning time, osmolality, limbal injection, the use of over-the-counter pain medications, tear film debris, and history of seasonal allergies. All the possible interactions were then added to these eight variables, and stepwise selection was used to develop the final model, with selection criterion set at $\alpha \leq 0.05$. No interactions were selected, and the final model included the following six variables, which are found in Table 5. As shown, nominal water content was most strongly related to dry eye status, followed by gender, PLTF thinning time, the use of over-the-counter pain medications, limbal injection, and osmolality. The Hosmer-Lemeshow goodness-of-fit test indicated excellent calibration ($\chi^2 = 8.24$, $P = 0.41$), and area under the ROC curve = 0.74 indicated acceptable discrimination.

DISCUSSION

Most would agree that successful contact lens wear depends on a stable tear film, including the production and maintenance of the constituents in each of its layers. Environmental conditions, lens parameters, tear film factors, or wearing schedules may impact the tear film structure during contact lens wear. This, in turn, may have clinical consequences such as contact lens–related dry eye symptoms, lens adherence, reduced tear exchange, contact lens dehydration, corneal desiccation, inflammatory events, and potentially sight-threatening infections.[49–57]

Tear Film and Contact Lens Factors

Several tear film factors were shown to be strongly related to contact lens–related dry eye in this study, and these factors are probably associated through a common mechanism. First, PLTF thinning time was significantly associated with dry eye status. The PLTF thinning time was approximately 2.8 seconds faster on average in those with dry eye than in those without dry eye. There are at least two potential mechanisms that may be associated with PLTF thinning time: evaporation and dewetting.[58] Contact lens–related dry eye typically maintains an "evaporative" classification (compared with a "tear-deficient" classification), and in part, the finding from this study supports this notion. However, tear film thinning times could also be explained by tangential flow or dewetting of the fluid due to surface tension gradients of the film or hydrophobic regions on the lens surface. Clinical intuition suggests that it is extremely

TABLE 3. Univariate Logistic Regression Analyses of Categorical Ophthalmic and Demographic Predictor Variables

Outcome	Dry Eye Frequency (%)	Non–Dry Eye Frequency (%)	Odds Ratio	95% CI	*P*
Gender					
Male	46 (40)	69 (60)	0.40	0.25–0.63	<0.0001
Female	153 (62)	92 (38)			
Lipid layer thickness					
Absent (0–13 nm)	21 (75)	7 (25)	0.79	0.69–0.91	0.0014
Open meshwork (13–50 nm)	48 (66)	25 (34)			
Closed meshwork (13–50 nm)	38 (61)	24 (39)			
Wave/flow (50–70 nm)	56 (47)	64 (53)			
Amorphous (80–90 nm)	16 (46)	19 (54)			
Colored fringe brown (90–140 nm)	13 (45)	16 (55)			
Colored fringe blue (>140 nm)	7 (54)	6 (46)			
Limbal injection					
None	136 (60)	91 (40)	0.73	0.53–1.01	0.06
Mild	48 (46)	56 (54)			
Moderate or severe*	15 (52)	14 (48)			
Tear Debris					
None	122 (54)	103 (46)	1.25	0.89–1.75	0.19
Mild	57 (53)	50 (47)			
Moderate or severe*	20 (74)	7 (26)			
Hydrogel ionicity					
Ionic (FDA groups 3–4)	83 (58)	60 (42)	1.21	0.77–1.92	0.41
Nonionic (FDA groups 1–2)	81 (53)	71 (47)			
Meibomian gland dropout					
1 (no partial glands)	100 (52)	91 (48)	1.11	0.86–1.44	0.43
2 (<25% partial glands)	64 (57)	49 (43)			
3 (25%–75% partial glands)	24 (62)	15 (38)			
4 (>75% partial glands)	6 (50)	6 (50)			
Lens Type					
Soft	20 (61)	13 (39)	0.79	0.38–1.63	0.52
Gas permeable	179 (55)	148 (45)			
Education					
Middle school (i.e., 7th–9th grade)	0 (0)	2 (100)	0.97	0.85–1.10	0.60
High school (10th–12th Grade)	46 (61)	30 (39)			
GED or equivalent	2 (100)	0 (0)			
Associate degree	4 (31)	9 (69)			
Bachelor's degree	102 (55)	84 (45)			
Master's degree	28 (58)	20 (42)			
Professional degree	8 (53)	7 (47)			
Doctorate degree	9 (50)	9 (50)			
Income					
Less than $14,999	33 (55)	27 (45)	0.98	0.85–1.07	0.64
$15,000 to $29,999	37 (56)	29 (44)			
$30,000 to $44,999	29 (52)	27 (48)			
$45,000 to $59,999	27 (68)	13 (33)			
$60,000 to $74,999	23 (62)	14 (38)			
$75,000 to $89,999	13 (42)	18 (58)			
$90,000 to $104,999	11 (46)	13 (54)			
More than $105,000	24 (56)	19 (44)			
Blink					
Complete	156 (55)	128 (45)	0.92	0.63–1.34	0.66
Incomplete	40 (61)	26 (39)			
Forced	1 (20)	4 (80)			
Twitch	2 (40)	3 (60)			
Bulbar injection					
None	66 (55)	54 (45)	1.00	0.75–1.33	0.99
Mild	93 (56)	74 (44)			
Moderate or severe*	40 (55)	33 (45)			

The probability is associated with the Wald χ^2 test of the hypothesis that the parameter of the logistic regression model is zero. The percentages presented sum for each outcome variable by row within each variable subclass.

* Due to infrequent observations of severe, the moderate and severe categories have been combined.

important for the contact lens to remain "wetted" with a coherent tear film over its surface, to provide good comfort, vision, lubrication; prevent surface drying; remove debris and particulate; and counter contamination and infection during lens wear. A lens that is nonwettable is also one that shows quick PLTF thinning time, as a wettable film spreads uniformly without breakup. Thus, although this study provides insight that PLTF thinning time is relevant, suggestion that evaporation is greater in lens wearers with dry eye cannot be made, as alternative mechanisms of thinning must be considered.

TABLE 4. Frequency Distributions of Categorical General Health-Related Predictor Variables of Factors Associated with Contact Lens–Related Dry Eye

Variable	Dry Eye Frequency (%)	Non–Dry Eye Frequency (%)	*P*
Allergies			
No	87 (48)	95 (52)	0.004
Yes	112 (63)	66 (37)	
OTC pain medications			
No	97 (51)	94 (49)	0.07
Yes	102 (60)	67 (40)	
Ophthalmic medication			
No	190 (54)	159 (46)	0.12
Yes	9 (82)	2 (18)	
Antihistamine use			
No	166 (53)	144 (47)	0.12
Yes	33 (66)	17 (34)	
OTC cough medications			
No	170 (54)	146 (46)	0.15
Yes	29 (66)	15 (34)	
Previous conjunctivitis			
No	104 (52)	96 (48)	0.17
Yes	95 (59)	65 (41)	
Hormone replacement therapy			
No	140 (61)	88 (39)	0.30
Yes	13 (76)	4 (24)	
Hypothyroid			
No	188 (55)	156 (45)	0.31
Yes	11 (69)	5 (31)	
Cholesterol medications			
No	188 (55)	156 (45)	0.31
Yes	11 (69)	5 (31)	
Postmenopausal			
No	131 (61)	83 (39)	0.33
Yes	22 (71)	9 (29)	
Antihypertensive medications			
No	187 (55)	155 (45)	0.34
Yes	12 (67)	6 (33)	
Diabetes			
No	191 (55)	158 (45)	0.36
Yes	8 (73)	3 (27)	
Hypertension			
No	181 (54)	151 (46)	0.43
Yes	18 (64)	10 (36)	
Retinopathy			
No	199 (55)	160 (47)	0.45
Yes	0 (0)	1 (100)	
Multivitamins			
No	103 (53)	96 (47)	0.46
Yes	96 (57)	71 (43)	
Asthma			
No	174 (54)	145 (46)	0.51
Yes	25 (61)	16 (39)	
Diuretic Medications			
No	192 (55)	158 (45)	0.52
Yes	7 (70)	3 (30)	
Cancer			
No	194 (56)	155 (44)	0.55
Yes	5 (45)	6 (55)	
Cataract			
No	193 (56)	154 (44)	0.58
Yes	6 (46)	7 (54)	
Heart disease			
No	198 (55)	159 (45)	0.59
Yes	1 (33)	2 (67)	
Osteoporosis			
No	198 (55)	159 (45)	0.59
Yes	1 (33)	2 (67)	
Arthritis			
No	179 (56)	142 (44)	0.61
Yes	20 (51)	19 (49)	
Tranquilizer medications			
No	177 (56)	140 (44)	0.62
Yes	22 (51)	21 (49)	

(*continues*)

TABLE 4. (*continued*). Frequency Distributions of Categorical General Health-Related Predictor Variables of Factors Associated with Contact Lens–Related Dry Eye

Variable	Dry Eye Frequency (%)	Non–Dry Eye Frequency (%)	*P*
Glaucoma			
No	196 (55)	160 (45)	0.63
Yes	3 (75)	1 (25)	
Sterile			
No	182 (55)	150 (45)	0.69
Yes	17 (61)	11 (39)	
Steroid medications			
No	195 (55)	159 (45)	0.69
Yes	4 (67)	2 (33)	
Arthritis medications			
No	196 (55)	157 (45)	0.70
Yes	3 (43)	4 (57)	
Retinal detachment			
No	196 (55)	157 (45)	0.70
Yes	3 (43)	4 (57)	
Hyperlipidemia			
No	178 (55)	146 (45)	0.73
Yes	21 (58)	15 (42)	
Sleep medication			
No	193 (55)	158 (45)	0.74
Yes	6 (67)	3 (33)	
Nasal steroids			
No	189 (55)	152 (45)	0.82
Yes	10 (53)	9 (47)	
Joint pain			
No	180 (56)	144 (44)	0.86
Yes	19 (53)	17 (47)	
Oral contraceptives			
No	102 (62)	63 (38)	0.89
Yes	51 (64)	29 (36)	
Diet medications			
No	87 (56)	69 (44)	0.91
Yes	112 (55)	92 (45)	
Lupus			
No	197 (55)	160 (45)	0.99
Yes	2 (67)	1 (33)	
Onset of menses			
No	1 (50)	1 (50)	0.99
Yes	152 (63)	90 (37)	
Macular degeneration			
No	198 (55)	160 (45)	0.99
Yes	1 (100)	0 (0)	

Probabilities were derived from the Fisher exact test. The percentages presented sum for each outcome variable by row within each variable subclass.

Also of importance is that the prelens lipid layer thickness in patients with dry eye tended to be less than in patients without dry eye. This outcome correlated highly with PLTF thinning time ($r = 0.60$, $P < 0.0001$), and so it did not remain significant in multivariate statistical modeling, although it certainly is important to consider in terms of a mechanistic model. These data do not support the idea of structural changes to the meibomian glands (via meibography) leading to altered or reduced meibum secretion that would yield a thinner than normal lipid layer. An alternative, more likely, explanation is that the polarity of the lipid head groups leads to electrostatic binding to the lens, and this surface deposition is probably associated with thin lipid layers, and increased evaporation (due to the altered lipid layer) and dewetting (due to the increased hydrophobicity of the surface).

TABLE 5. Multivariate Logistic Regression Analyses of Predictor Variables of Factors Associated with Contact Lens–Related Dry Eye

Variable	Odds Ratio	95% CI	*P*
Nominal water content	1.03	1.01–1.05	0.002
Gender (female)	2.25	1.24–4.06	0.007
PLTF thinning time	0.95	0.91–0.99	0.008
Over-the-counter pain medication usage	2.00	1.13–3.52	0.02
Limbal injection	0.59	0.36–0.96	0.03
Osmolality	1.01	1.00005–1.02	0.05

An increase in tear film osmolality was also significantly associated with dry eye status. In this regard, the average osmolality for those with dry eye was 307.66 mOsM, whereas the average for those without dry eye was 297.06 (~10 mOsM difference). These values are slightly lower than might be expected from a review of the literature, and may be correct, as all subjects were required to remove their lenses before osmolality measures, which may have lead to some reflex tearing that lowered the observed values across both groups. Regardless, this is an important finding, as osmolality is often considered to be a gold standard diagnostic test, in addition to an etiological factor, associated with dry eye disease in general

through proinflammatory mechanisms.[59,60] Gilbard et al.[28] suggested that increased osmolality is the hallmark characteristic of contact lens–related dry eye, which in part has created some controversy relative to this topic through the years. Osmolality can be measured by only a handful of research groups worldwide and thus, this proposed mechanism has not been consistently replicated. Gilbard et al. suggest that "decreased corneal sensitivity, with a resultant decrease in tear secretory rates, is the most likely cause for increased tear-film osmolality. . . ."[28] Although the mechanism of increased osmolality cannot necessarily be directly derived from these data, a viable explanation might be related to tear film evaporation. As patients with dry eye in this sample had a reduction in the lipid layer thickness, they may be more susceptible to evaporation of the prelens tear film than those patients without dry eye. An increase in tear film evaporation may lead to a more concentrated tear film and a resultant increased osmolality. The idea of increased osmolality related to insufficient tear production, as measured by the phenol red thread test, was not supported.

One of the more contentious factors potentially associated with contact lens–related dry eye has been the nominal water content (and refractive index) of a lens and associated lens dehydration. The refractive index of a low-water-content contact lens is higher than that of a high-water-content lens, and dehydration results in an increase in refractive index in this regard. Generally, low-water-content lenses may lose approximately 1% of their water content, and high-water-content lenses may lose up to approximately 5%.[61,62] For years, clinicians have relied on the theoretical argument that a result of evaporation is lens dehydration with resultant drying of the eye. This study provides evidence that patients using lower-water-content hydrogel lenses (and, thus, higher refractive index hydrogel lenses) are less likely to be those with dry eye. Nominal refractive index and water content are highly correlated ($r = -0.87$, $P < 0.0001$), as are measured water content and refractive index ($r = -0.95$, $P < 0.0001$) and thus, only nominal water content is maintained in the final multivariate statistical model. However, these data do not show that lens dehydration is related to contact lens–related dry eye. Several smaller-scale studies have evaluated contact lens dehydration and patients' symptoms, with varied results.[21,50,63,64] Efron and Brennan[63] found that patients wearing low-water-content lenses that maintained their hydration (compared with low water content lenses that dehydrated) generally reported that their eyes never felt dry during lens wear. Pritchard and Fonn[21] examined the dehydration of three different water content hydrogel lenses and the relation of this dehydration to lens movement, diameter changes, and dryness symptoms. They found no correlations between dehydration, movement, diameter, and dryness symptoms. Finally, Fonn et al.[50] performed a similar study, but used two groups of patients—one with symptoms of dryness and the other without such symptoms—showing no relation between lens dehydration and dryness, comfort, or tear film thinning time. Thus, the evidence to date seems to suggest that although high-water-content (low refractive index) lens use may be associated with contact lens–related dry eye symptoms, dehydration of these lenses does not seem to be the mechanism associated with the symptoms. It may indeed be that the polar head groups associated with the tear film lipid molecules are attracted to lenses of higher water content, leaving their nonpolar tails extended away from the lens surface, leading to evaporation and/or dewetting. This idea is supported by both the PLTF thinning time reduction and thinned lipid layer found in patients with dry eye.

Patient-Related Factors

Unlike other sociodemographic variables, gender (women) was significantly related to dry eye status. This finding was true, even after including this term in multivariate statistical modeling, which in essence, controls for tear film-related factors. In other non–contact lens dry eye studies, others have also found that women are between 1.5 and 2 times more likely to report dry eye disease as are men.[2,4,6,7] There are two potential explanations for this finding. First, in women there are obviously various endogenous hormonal factors that may affect dry eye status relative to men. Examples of these factors include monthly menstrual cycling, oral contraceptive use, menopause, and use of hormone replacement therapy. The relation of these to dry eye disease in general is only starting to be understood and certainly could be implicated in our study. However, the use of hormone replacement therapy or oral contraceptives was not related to contact lens–related dry eye in this study. A second potential explanation associated with this finding may be related to the finding of previous studies indicating that women seem to be more likely to report symptoms of disease than are men.[65–68] This has been shown to be true after controlling for disease status differences through objective measures of disease, similar to our finding in which we controlled for differences in tear film and contact lens–related factors in the multivariate analysis.[69] Also of interest is that patients reporting the frequent use of over-the-counter pain medications were more likely to self-report dry eye. Although the mechanism of this is unclear, it could be that these patients are generally more symptomatic relative to their health and looking for relief of their symptoms.

In summary, several tear film and contact lens–related factors were shown to be associated with dry eye status in contact lens wearers. Particularly novel in this research are the findings that a reduction in lipid layer thickness, rapid PLTF thinning, and high-water-content hydrogel lens usage are predictive of contact lens–related dry eye, whereas contact lens dehydration was shown not to be related to dry eye in lens wearers, contrary to long-held belief. This information is important, as it provides insights into potential mechanisms of contact lens–related dry eye, such that its prevention can be targeted. This is particularly true as new materials, such as silicone hydrogels, are introduced to the market, given their unique issues associated with biocompatibility.

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