Not All Dry Eye in Contact Lens Wear Is Contact Lens–Induced

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Objectives: To compare subjective and clinical outcomes in three study groups: (1) asymptomatic contact lens (CL) wearers (ASYM); (2) symptomatic CL wearers who become asymptomatic on lens removal; and (3) symptomatic CL wearers who do not resolve on lens removal.

Methods: Ninety-two subjects completed the Berkeley Dry Eye Flow Chart with and without lenses, ocular surface examinations, and a battery of questionnaires.

Results: Thirty-seven subjects (40%) were ASYM, 30 (33%) had contact lens–induced dry eye (CLIDE), and 25 (27%) had underlying physiological DE. Visual Analog Scale ratings, OSDI score, and SPEED score were significantly better for the ASYM group ($P<0.001$) but did not distinguish CLIDE from DE. The DE group was significantly worse than CLIDE and ASYM, which were similar, in precorneal noninvasive tear breakup time (8.2 sec DE vs. 12.3 sec CLIDE and 14.3 sec ASYM; $P=0.002$), anterior displacement of the Line of Marx ($P=0.017$), and superior conjunctival staining ($P=0.001$).

Conclusions: Many CL wearers presenting with dryness symptoms have an underlying DE condition and will not respond to treatments aimed at changing lenses or solutions. Contradictory results from research studies of DE in CL wearers could be due in part to a failure to distinguish subjects with symptoms due specifically to CL wear from those whose symptoms have underlying causes unrelated to CL wear.

Key Words: Dry eye—Tear breakup time—Soft contact lenses—Symptom questionnaires—Line of Marx—Conjunctival staining.

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Dry eye associated with contact lens (CL) wear is one of the most common causes of CL dissatisfaction and discontinuation. Of the estimated 35 million CL wearers in the United States, dry eye (DE) symptoms have been reported in 15% to 79% of wearers,[1–9] and between 12% and 51% per year discontinue wear.[10] In the clinical setting, attempts to alleviate contact lens–induced dry eye (CLIDE), for example, by changing lens fit parameters or materials, can yield unsatisfactory results when knowledge of the specific causes of the complaint is inadequate. In the research setting, a surprisingly large majority of studies of dryness in CL wear make no mention of any determination of underlying causes, for example, by using eligibility criteria that accept any "symptomatic" CL wearer as an eligible subject, or that accept wearers who score above a certain threshold on one of the many available DE questionnaires.[4,6,9,11–18] Although it may be tempting to accept at face value a complaint of the eyes feeling dry while wearing lenses, as discussed in the report of the TFOS International Workshop on CL Discomfort,[10] currently, such symptoms largely define the condition, and our understanding of its etiology is still evolving. In that report, CL-related dryness is considered a type of CL discomfort, or several subtypes with different mechanisms, distinct from (but in some cases related to) physiological DE disease. Clearly, further work in distinguishing and classifying ocular discomfort and dryness symptoms and their etiologies is needed. We do know that failing to investigate the underlying causes and identifying more carefully the DE subtype(s) presenting, to the best of our current ability, can lead to misplaced and ineffective treatments in the clinic and to equivocal results for ill-defined study populations in a clinical trial setting.

A currently undocumented percentage of CL wearers with dryness symptoms may have an underlying physiological DE condition and not simply a reaction to lens wear and will not necessarily respond well to treatments aimed at changing CL fit, material, or care solutions. It is important to determine what patient's symptoms are both with and without CL wear for better targeted treatment and to make this same determination when selecting subjects for clinical study for a clearly defined study population. Among all CL wearers with dryness complaints, there are likely to be cases in which DE symptoms are caused directly by lens wear, cases in which underlying physiological DE is present and perhaps exacerbated by lens wear, and even cases in which symptoms can be relieved with CL wear. In patients with lagophthalmos, for example, a CL can improve dryness symptoms by acting as a bandage, retaining a tear reservoir and isolating the corneal surface from the external environment.[19,20] Those whose symptoms are relieved after CL removal may be considered genuinely to have CLIDE and may benefit from changes in CL material,[10,21] or care systems.[22] Those whose dryness symptoms persist both with and without CL wear likely have an underlying DE condition that needs to be treated to be successful with CL wear.

The primary aim of this study is to compare subjective and clinical outcomes in three study groups: (1) asymptomatic CL wearers (ASYM); (2) symptomatic CL wearers who become asymptomatic with lenses removed (CLIDE); and (3) CL wearers who are symptomatic both with and without lenses (DE). The results of this study may help to diagnose DE related to CL wear to appropriately manage and treat patients' symptoms, reduce the likelihood of future CL drop out, better define populations under

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clinical study, and reduce the likelihood of equivocal results in clinical trials due to aggregating different subtypes of symptomatic subjects who may respond to interventions or exposures differently or not at all.

METHODS

Subjects

This study analyzes data from a multistudy database of CL studies conducted at the University of California (UCB) Clinical Research Center. Subjects were recruited from the UCB campus and surrounding community to participate in one or more 1-day, on-site studies. All studies contributing to the database used identical eligibility criteria, and subjects underwent the same procedures in the same order. Eligibility criteria included being 18 years of age or older, being a full-time CL wearer (8 or more hr per day, 5 or more days per week, continuously for at least the previous 1 month), and having no active ocular surface pathology, history of ocular surgery, or currently taking medications that could affect the ocular surface or tear film. The study adhered to the tenets of the Declaration of Helsinki, and the protocol was approved by the UCB Committee for Protection of Human Subjects. All study participants were recruited from the UCB campus and neighboring community.

Before clinical examinations and instrument measurements, a battery of five questionnaires was administered in randomized order to avoid potential temporal bias in responses due to progressive subject fatigue or patterning of responses. A Williams Pair[23,24] was constructed of two first-order carryover balanced Latin Squares that were interlaced, split, and then randomly permuted to determine questionnaire ordering. This can be a useful alternative to standard randomization when the number of possible random orderings exceeds the anticipated number of subjects. The questionnaire battery consisted of the Berkeley Dry Eye Flow Chart (Berkeley DEFC),[25] the Contact Lens Dry Eye Questionnaire (CLDEQ-8),[1,26] the Ocular Surface Disease Index (OSDI),[27] the Standard Patient Evaluation of Eye Dryness (SPEED),[28] and a 100-point Visual Analog Scale (VAS) rating questionnaire for average and end-of-day severity and frequency of CL discomfort and dryness.[29,30]

To define the subject groups for this study, a follow-up questionnaire (i.e., not part of the randomized battery) ascertained the DEFC score with lenses removed. The DEFC for CL wearers has been described and validated elsewhere.[25] In brief, the DEFC is a five-point ordinal scale with a score of one indicating no dryness symptoms at all, two indicating some dryness but without causing discomfort, and three through five indicating dryness causing sufficient discomfort to interfere with visual activities such as reading, using a computer, or wearing contact lenses, never, sometimes, and usually/always, respectively. Subjects scoring a one or two both with and without lenses were categorized as ASYM. Subjects scoring a four or five both with and without lenses were categorized as DE. Subjects scoring a four or five with lenses on and scoring a one or two with lenses removed were categorized as CLIDE. For this retrospective database analysis, every subject who responded to the follow-up questionnaire and could be categorized according to these criteria (e.g., excluding those who scored a three on the DEFC), and who had completed all study measurements, was included in the analysis (n=92).

After administration of the subjective response instruments, a comprehensive ocular surface examination was performed, and instrument measurements were taken. Procedures were performed from noninvasive to invasive. The mean tear lipid layer thickness and coefficient of variation and the number of partial and total blinks during a 30-sec scan were acquired using the LipiView ocular surface interferometer (TearScience, Morrisville, NC). Noninvasive tear breakup time (NITBUT) was measured using the Medmont E300 corneal topographer (Medmont Pty Ltd, Nunawading, Australia) and a stopwatch. After instillation of sodium fluorescein, the subject was positioned at the slitlamp, corneal staining was graded on the SICCA scale,[31] and fluorescein tear breakup time (FTBUT) was measured. Conjunctival staining with lissamine green was then graded. A Korb Meibomian Gland Evaluator (TearScience) was used to express the Meibomian glands, and the quantity and quality of the expressate were scored similarly to previously publications.[32,33] The position of the Line of Marx was graded on the scale of Yamaguchi et al.,[34] and the length and width of any observed lid wiper epitheliopathy was graded according to the scale of Korb et al.[35] Meibography images of the upper and lower lids were taken using an Oculus Keratograph 5M (Oculus, Inc., Arlington, WA).

Statistical Methods

After a thorough descriptive analysis, linear mixed-effects analysis of variance models were fit to determine whether questionnaire outcomes, clinical assessments, and laboratory measurements differed significantly among the ASYM, DE, and CLIDE groups. Eyes were modeled as varying randomly within subjects, with subjects independent. Models were assessed by considering the F-test *P* values, the clinical importance of estimated effect sizes, and residual and other diagnostic plots. Invasive FTBUT and NIBUT were modeled on the natural log scale to better approximate normality of residuals. For ordinal categorical outcomes, the χ^2 test was used to test the independence of score distribution from symptom group. For ordinal scores that were significantly related to study group, methods from correspondence analysis[36] were used to gain further insight. Tukey's Honestly Significant Difference was used for multiple comparisons while maintaining an overall familywise $\alpha=0.05$.[37]

RESULTS

Subject Characteristics

Of the n=92 subjects who met the inclusion criteria, 37 (40%) were classified as ASYM, 30 (33%) were classified as CLIDE, and 25 (27%) were classified as DE. The ages of the subjects in this study ranged from 18 to 61 years, with a mean (SD) age of 26.3 (9.5) years. Subjects were approximately 76% female and 24% male and were approximately 61% of Asian ethnicity and 39% non-Asian. The Asian group consisted of subjects of Chinese, Japanese, Vietnamese, and Korean ethnicity. The non-Asian group consisted primarily of white subjects, with a minority of African American, Latino, and Indian subjects. Years of CL wear across all groups ranged from just over the minimum eligible 1 month up to 43 years, with a mean (SD) of 11.0 (8.0) years. Habitual CL spherical power ranged from −0.50 D to −12.00 D with cylinder power ranging from 0 D to −2.25 D.

There were no significant differences between the ASYM, CLIDE, and DE groups in age, sex, ethnicity, years of CL wear, CL prescription, proportion of allergy sufferers, or proportion reporting past treatment for acne. It is perhaps notable that while Asian subjects comprised 50% of the ASYM group and 57% of the CLIDE group, they comprised 80% of the DE group. This difference between groups in proportion of Asian subjects was, however, not significant at the $\alpha=0.05$ level ($P=0.061$).

Lipid Layer, Tear Film, and Ocular Surface

Lipid layer, tear film, and ocular surface results stratified on symptom group are summarized in Table 1. Precorneal NITBUT was significantly shorter ($P=0.002$) in the DE group compared with the ASYM and CLIDE groups which averaged similar breakup times (8.18 sec DE vs. 12.26 sec CLIDE and 14.32 sec ASYM). Adjustment for multiple comparisons showed the DE group to be significantly different from both the ASYM and CLIDE groups. Qualitatively, NITBUT averaged longer than the standard clinical criterion for a stable tear film of 10 sec in both the ASYM and CLIDE groups, while the DE group averaged under the clinically acceptable threshold. Fluorescein tear breakup time was also significantly different among the three subject groups overall ($P=0.006$), and although the same general pattern as for NITBUT held, adjustment for multiple comparisons showed that the DE group (5.54 sec) was significantly different in mean FTBUT from the ASYM group (9.97 sec) but not from the CLIDE group (8.37 sec).

There were significant differences in the number of partial blinks that occurred during the 30-sec LipiView scan ($P=0.003$), with the CLIDE group averaging the fewest at 3.6 blinks/30 sec, followed by the ASYM group with 4.9 blinks/30 sec, and the DE group at 6.4 blinks/30 sec.

There was a statistically significant difference in the clinical grade of superior conjunctival staining with lissamine green ($P=0.001$); however, the intergroup differences were of marginal clinical significance, with the ASYM, CLIDE, and DE groups averaging grades of 0.09, 0.21, and 0.55, respectively, on the 0 to 4 grading scale. There were no significant differences in conjunctival staining in the other quadrants.

There were no significant intergroup differences in mean lipid layer thickness, variability in lipid layer thickness, total number of blinks (partial and complete) during LipiView scanning, tear meniscus height, Schirmer I test strip wetted length, grade of bulbar or limbal hyperemia, or grade of corneal staining.

Meibomian Glands and Eyelids

Table 2 summarizes the results of the Meibomian gland and lid evaluations stratified on symptom group. There was a significant intergroup difference in the anterior displacement of the upper lid Line of Marx ($P=0.017$), with significantly greater displacement on average in the DE group, and with the ASYM and CLIDE groups being similar. There was a similar pattern for the lower lid, but it was not statistically significant ($P=0.101$). Figure 1 depicts the anterior displacement grading of the upper lid Line of Marx in a balloon plot. This type of data visualization is used to gain additional insight into significantly related categorical variables. The marginal totals for rows and columns are shown, along with circular "balloons" that are proportional in size to the cell counts. Looking down the first column of Figure 1, it can be seen that the most grades of 0 occur in the ASYM group followed by the CLIDE group, with the fewest grades of 0 in the DE group; by contrast, looking down the third column shows relatively few grades of 2+ in the ASYM group

TABLE 1. *Lipid Layer, Tear Film, and Ocular Surface*

	ASYM		CLIDE		DE		
Variable	Mean	SD	Mean	SD	Mean	SD	*P*
Lipid layer thickness (nm)							
Mean	63.5	15.5	66.5	20.6	61.0	19.4	0.299
Maximum	79.2	15.5	79.7	18.5	73.7	18.8	0.147
Minimum	56.1	16.7	58.6	21.6	53.1	19.7	0.339
CV	0.07	0.03	0.07	0.03	0.06	0.03	0.820
Partial blinks (n)	4.9	4.6	3.6	2.7	6.4	4.6	0.003
Total blinks (n)	6.3	4.5	6.6	4.3	8.0	4.4	0.119
Noninvasive TBUT (sec)	14.32	11.32	12.26	9.68	8.18	4.10	0.002
Fluorescein TBUT (sec)	9.97	9.16	8.37	7.42	5.54	3.47	0.004
Tear meniscus height (mm)	0.25	0.08	0.25	0.08	0.25	0.07	0.893
Schirmer I test (mm)	19.32	9.63	20.68	10.27	17.20	8.03	0.224
Conjunctival staining (0–4)							
Nasal	0.80	0.85	1.02	1.02	1.10	1.19	0.279
Temporal	0.44	0.53	0.60	0.91	0.68	0.94	0.289
Superior	0.09	0.29	0.21	0.54	0.55	0.99	0.001
Inferior	0.33	0.51	0.35	0.65	0.50	0.88	0.416
Bulbar hyperemia (0–16)	2.43	1.93	2.34	1.92	2.26	2.35	0.898
Limbal hyperemia (0–16)	1.41	1.95	1.82	1.95	1.54	1.99	0.490
Corneal staining (0–20)							
Type	0.85	1.53	0.61	0.85	1.26	1.88	0.068
Extent	0.69	1.63	0.46	0.71	0.65	0.83	0.512
Depth	0.67	1.18	0.53	0.72	0.93	1.11	0.121

DE subjects had significantly shorter invasive and noninvasive tear breakup times, and significantly more partial blinks during lipid layer imaging, compared with ASYM and CLIDE subjects, who were similar. Superior conjunctival staining was worse, on average, in the DE group, followed by the CLIDE group and then the ASYM group with the least conjunctival staining.

CLIDE, contact lens–induced dry eye; CV, coefficient of variation; DE, dry eye; TBUT, tear breakup time.

TABLE 2. *Meibomian Glands and Eyelids*

	ASYM		CLIDE		DE		
Variable	Mean	SD	Mean	SD	Mean	SD	*P*
Blepharitis							
Upper lid	1.03	1.03	0.75	0.62	0.65	0.80	0.060
Lower lid	0.77	0.99	0.35	0.52	0.23	0.42	<0.001
Line of Marx							
Upper lid	0.61	0.72	0.62	0.76	0.98	0.85	0.017
Lower lid	0.77	0.75	0.65	0.73	0.96	0.78	0.101
Lid wiper epi							
Length (mm)	0.62	1.03	0.93	1.25	1.04	1.23	0.109
Width (mm)	0.43	0.80	0.68	0.93	0.88	1.17	0.036
MG expressate							
Upper, quantity	16.76	15.16	20.28	17.07	19.30	15.10	0.416
Upper, quality	14.11	14.67	16.60	14.75	14.78	13.59	0.641
Lower, quantity	17.49	15.01	20.95	13.22	19.60	14.08	0.370
Lower, quality	14.70	14.91	16.38	11.27	15.70	13.11	0.789
MG atrophy							
Upper	0.61	0.68	0.71	0.59	0.60	0.57	0.553
Lower	0.55	0.78	0.43	0.66	0.70	0.79	0.177
Lagophthalmos	No: 42 (58.3%)	Yes: 30 (41.7%)	No: 33 (55.0%)	Yes: 27 (45.0%)	No: 36 (72.0%)	Yes: 14 (28.0%)	0.217

Anterior displacement of the Line of Marx in the upper lid was significantly greater in the DE group compared with the ASYM and CLIDE groups which were similar. Width of lid wiper epitheliopathy was significantly different among groups, with the greatest width in the DE group, followed by the CLIDE group, then the ASYM group.

CLIDE, contact lens–induced dry eye; DE, dry eye; Epi, epitheliopathy; MG, Meibomian gland.

and the most in the DE group. Looking across the rows, one can see that although the ASYM and CLIDE groups have mostly grades of 0 and 1 (with a few more grades of 2+ in the CLIDE group), the DE group shows a different pattern with nearly the same number of 2+ grades as 0 or 1 grades.

A significant intergroup difference in lid wiper epitheliopathy was found for width (P=0.036) but not for length (P=0.109). Mean grade of lid wiper epitheliopathy width was greatest in the DE group (0.88), followed by the CLIDE group (0.68) and the ASYM group (0.43). Multiple comparison analysis showed that only the two extreme groups, ASYM and DE, were significantly different, while the CLIDE group averaged in between them and was not significantly different than either. The asymmetric biplot in Figure 2 depicts the association of lid wiper epitheliopathy grade with symptom group.[36] This data visualization technique is used in correspondence analysis, a type of principle components analysis for contingency tables. A full discussion of this type of analysis is outside the scope of this article; suffice it to say that in this dimension reduction technique, the axes reflect the proportions of variability explained by the rows (i.e., the three study groups), and the proximity of the vector arrow for each study group (ASYM, CLIDE, and DE) to the vectors for the different lid wiper epitheliopathy grades reflects the strength of association of each study group with certain clinical grades. The figure shows the ASYM group arrow aligning most closely to a grade of 0, the CLIDE group arrow to grades 1 and 2, and the DE group arrow to a grade of 3.

There was a significant intergroup difference in grade of lower lid blepharitis (P<0.001). Curiously, the highest mean grade of lower lid blepharitis was found in the ASYM group (0.77), followed by the CLIDE (0.35) and DE (0.23) groups.

There were no significant differences among symptom groups in quality or quantity of Meibomian gland expressate for either the upper or lower lid, grade of Meibomian gland atrophy, or proportion of subjects exhibiting lagophthalmos.

Subjective Symptoms with Habitual Contact Lenses

Table 3 summarizes the subject responses to the questionnaire battery stratified on the symptom group. There were significant intergroup differences for all instruments. In general, the ASYM

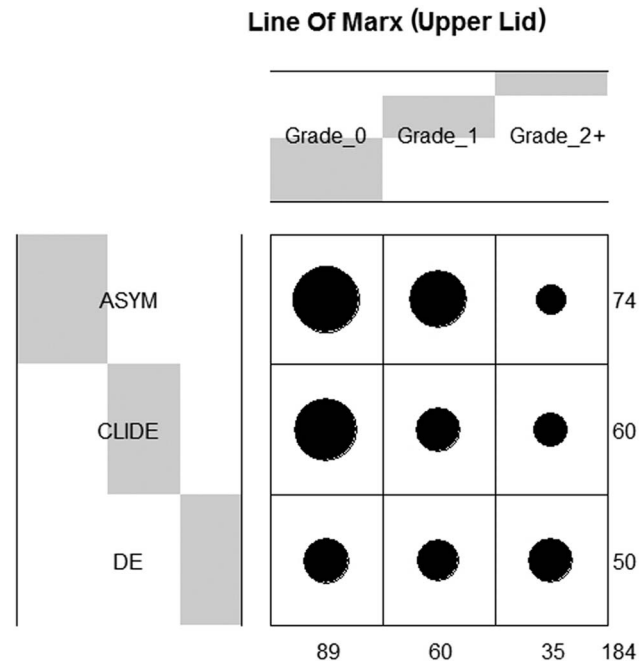

FIG. 1. Anterior displacement (grade) of the Line of Marx in the three symptom groups. There was significantly greater displacement on average in the DE group, with the ASYM and CLIDE groups being similar. It can be seen in this balloon plot that the fewest grade 0 and the most grade 2+ upper lid Line of Marx displacements were found in the DE group. CLIDE, contact lens–induced dry eye; DE, dry eye.

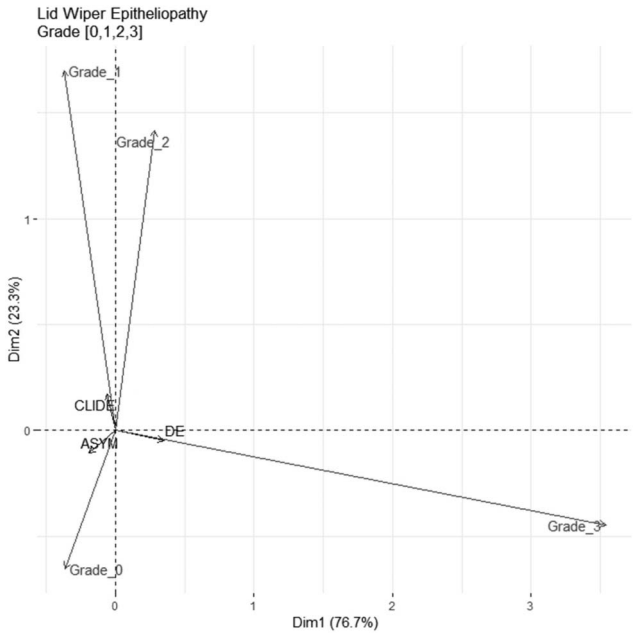

FIG. 2. Width of upper lid wiper epitheliopathy (grade) in the three symptom groups. Mean grade of lid wiper epitheliopathy width was greatest in the DE group (0.88), followed by the CLIDE group (0.68) and the ASYM group (0.43). In this asymmetric biplot, the closer a symptom group arrow aligns to the arrow for a grade, the stronger the association. The figure shows the ASYM group most strongly associated with a grade of 0, the CLIDE group with grades of 1 and 2, and the DE group with a grade of 3. CLIDE, contact lens–induced dry eye; DE, dry eye.

group had better comfort and less dryness than either the CLIDE or DE groups. The CLIDE and DE groups tended to have similar outcomes, or for some instruments, the DE group had moderately worse symptom ratings than the CLIDE group, on average. Figure 3 depicts representative examples of the 11 questionnaires administered (i.e., in addition to the DEFC, which was used for classifying subjects into symptom groups). Visual Analog Scale ratings (0–100 scale) for severity of end-of-day dryness averaged 9.82 in the ASYM group, while averaging 47.31 in the CLIDE group and 49.70 in the DE group ($P<0.001$). Frequency of end-of-day dryness on the VAS averaged 11.73 for the ASYM group, while averaging 48.73 for the CLIDE group and 48.30 for the DE group ($P<0.001$). The OSDI score averaged 4.72 in the ASYM group, while averaging 16.92 in the CLIDE group and 20.48 in the DE group. Similar results were found for average VAS ratings of severity and frequency of dryness, VAS ratings of the frequency of discomfort, and SPEED score (all $P<0.001$). Multiple comparison adjustments found that for these instruments, ASYM subjects were significantly different in subjective response than both CLIDE and DE, which were not significantly different from each other.

For some subjective instruments, multiple comparison adjustments found all three symptom groups to be significantly different from one another, with the ASYM group having the best outcomes on average, followed by the CLIDE group, then the DE group with the worst outcomes on average. These included VAS ratings of average severity of discomfort, VAS ratings of end-of-day severity and frequency of discomfort, and CLDEQ-8 score (all $P<0.001$).

DISCUSSION

In this study, we investigated subjective and clinical outcomes in asymptomatic CL wearers, symptomatic CL wearers who are asymptomatic with lenses removed, and CL wearers who are symptomatic both with and without lenses. A surprisingly large number of published studies related to DE in CL wear do not adequately define their criteria for an eligible, symptomatic subject, nor the means by which such subjects are recruited and retained in the study, resulting in ill-defined study populations and possibly unwarranted generalizations of results.[38] In the clinical setting, time and effort are routinely wasted pursuing mistargeted solutions to CL-related dryness problems that are unlikely to produce the desired results because CLIDE and physiological DE are not the same.[39,40] In many cases, a lack of in-depth investigation into the subtypes, causes, and contributing factors of the presenting DE results in dissatisfaction for the patient and a risk of discontinuation of lens wear. In this study, we investigated specifically how an array of subjective response instruments, clinical assessments, and laboratory measurements might differ between not just asymptomatic and symptomatic CL wearers, but also between those wearers whose symptoms are likely the direct result of CL wear and those whose symptoms more likely stem from an underlying physiological DE problem.

Subjective response instruments were found generally to have significantly different outcomes between the asymptomatic group and the two symptomatic groups collectively, but not to differentiate well between CLIDE and DE. In particular, all VAS ratings of dryness severity and frequency, on average and at end-of-day, were lower for the asymptomatic group and higher and nearly identical for CLIDE and DE, as were OSDI and SPEED scores, as well as VAS rating for average frequency of discomfort. Visual Analog Scale ratings of dryness, OSDI, and SPEED seem to be reliable questionnaire instruments to screen for DE symptoms[27,28] but are unable to determine whether DE is due to CL wear or underlying DE disease. This highlights the importance of administering subjective response instruments to CL wearers to determine symptoms both with and without lenses on. By contrast, VAS ratings of average severity of discomfort, VAS ratings of end-of-day severity and frequency of discomfort, and the CLDEQ-8 score were found to be significantly different in all three symptom groups. This suggests that these instruments could be used to distinguish DE subtypes among symptomatic CL wearers; however, further study is required with larger sample sizes to determine their diagnostic performance (e.g., sensitivity, specificity, and positive predictive value) and appropriate diagnostic thresholds.

Among the clinical assessments and laboratory measurements, precorneal NITBUT most clearly differentiated between CLIDE and DE. It is interesting to note that with lenses removed, CLIDE subjects did not have significantly shorter NITBUT than completely asymptomatic subjects, while DE subjects had significantly shorter NITBUT than both. Alzahrani et al.[41] reported similarly close mean NITBUT in asymptomatic and CLIDE subjects. In that study, neophytes with no underlying physiological DE, as defined by having a score ≤6 on the DEQ-5 questionnaire and meeting published thresholds on at least one of NITBUT (≥9 sec), the phenol red thread test (>10 mm) or corneal staining grade (<2), were fit with daily disposable contact lenses, and CLIDE was defined as having a score above 17 on the

TABLE 3. *Subjective Symptoms*

	ASYM		CLIDE		DE		
Variable	Mean	SD	Mean	SD	Mean	SD	*P*
VAS—avg comfort	93.48	7.05	76.50	15.81	66.30	20.20	<0.001
VAS—discomfort							
Avg frequency	6.91	5.59	27.58	19.814	32.85	23.75	<0.001
VAS—EOD comfort	86.03	17.33	61.19	24.60	47.85	25.83	<0.001
VAS—discomfort							
EOD frequency	9.09	10.13	36.81	24.92	48.60	26.31	<0.001
VAS—Dryness							
Avg severity	10.91	17.55	36.69	23.07	41.55	25.76	<0.001
Avg frequency	8.45	11.61	35.08	25.80	36.45	25.76	<0.001
EOD severity	9.82	9.76	47.31	28.22	49.70	29.75	<0.001
EOD frequency	11.73	12.89	48.73	29.18	48.30	26.99	<0.001
CLDEQ-8	6.91	4.16	14.81	3.94	18.60	5.30	<0.001
OSDI	4.72	5.14	16.92	15.29	20.48	16.45	<0.001
SPEED	3.05	2.82	8.27	4.14	9.00	4.19	<0.001

CLIDE and DE subjects reported similar symptoms on average, compared with ASYM subjects. The two dry eye subtypes cannot be distinguished based on these questionnaire instruments alone. Intergroup differences were significant for all instruments.

Avg, average throughout the day; EOD, end-of-day; CLDEQ-8, Contact Lens Dry Eye Questionnaire 8 (score 0–37); DE, dry eye; OSDI, Ocular Surface Disease Index (score 0–100); SPEED, Standard Patient Evaluation Of Eye Dryness (score 0–28); VAS, Visual Analog Scale (rating scale 0–100).

CLDEQ-8 questionnaire after one week of wear. To the best of our knowledge, the current study is the first to report that the greater tear film instability commonly observed in groups of symptomatic CL wearers[42] is likely being driven by those subjects with an underlying DE condition, and that subjects with truly CL-induced symptoms average about the same precorneal NITBUT as asymptomatic wearers.

Grade of lid wiper epitheliopathy width was lowest on average among asymptomatic lens wearers, and highest among those with DE; subjects with CLIDE were graded in between those two

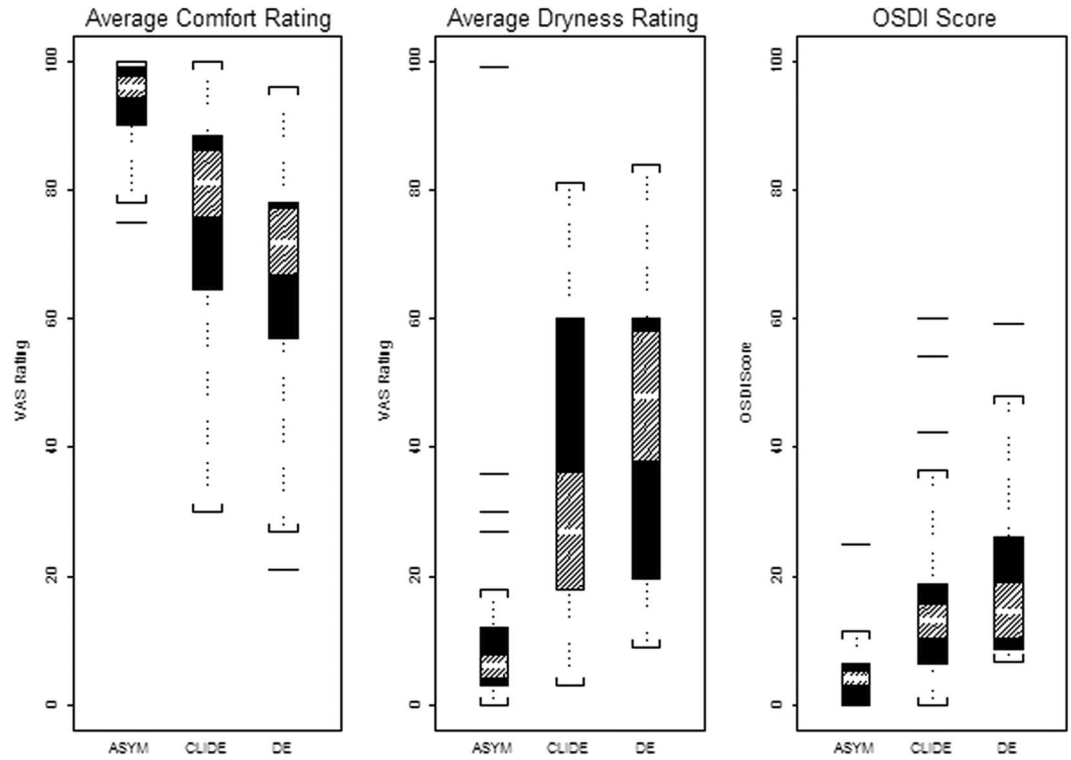

FIG. 3. Representative subjective response ratings in the three symptom groups. Shown are VAS ratings for average comfort and dryness severity and OSDI score. In general, scores on subjective instruments showed both the CLIDE and DE groups to have significantly worse symptoms than the ASYM group, but not to be distinguishable from one another based on symptom reporting alone. CLIDE, contact lens–induced dry eye; DE, dry eye; OSDI, Ocular Surface Disease Index; VAS, Visual Analog Scale.

groups, on average. After adjusting for multiple testing, however, it was found that only the ASYM and DE groups were significantly different, and CLIDE was not significantly different from either ASYM or DE. Some studies have shown lid wiper epitheliopathy to be associated with dryness symptoms both with and without CL wear,[35,43] although not all studies have confirmed this relationship.[44] It should be noted that the presence of a CL, with its higher coefficient of friction compared with the ocular surface and its significant association with lid wiper epitheliopathy,[43] might lead one to expect a higher grade on average in the CLIDE group. However, in the current study, although there was a significant difference between the ASYM and DE groups only, all three groups averaged <1 on the 0 to 4 grading scale for lid wiper epitheliopathy width, and thus, the magnitude of the difference is not of clinical importance, in agreement with previous studies.[45] The presence of lid wiper epitheliopathy may be related to symptoms in CL wearers, but it is a poor differentiator between CLIDE and DE. Although some research suggests that the relationship between lid wiper epitheliopathy and dryness symptoms may be dependent to an extent on the lens material worn,[46] further study is needed to determine whether lid wiper epitheliopathy could better differentiate DE from CLIDE if the type of lens material were taken into account.

There is a lack of consensus as to whether or not CL wear affects Meibomian gland function with several studies showing correlation between poor Meibomian gland expressibility and CL wear,[47–49] while other studies report no such correlation.[50–52] Regardless, in evaluating the Line of Marx, its placement is an important indicator of Meibomian gland dysfunction when assessing the cause of DE.[38,53] In the current study, the DE group had the greatest average anterior displacement of the Line of Marx, with displacement approximately the same in the CLIDE and ASYM groups. This suggests that anterior displacement of the Line of Marx could be an important factor in differentiating between DE and CLIDE. The Line of Marx is more likely an indicator of underlying DE disease with CL wear than just CL wear itself. Conversely, CL-related symptoms with normal NITBUT and without displacement of the Line of Marx point more to CLIDE and suggest that treatments aimed and changing lens brands, materials, fit, wearing modality, or care systems could be helpful in alleviating symptoms.

Superior conjunctival staining with lissamine green was significantly worse in the DE group than in the CLIDE and ASYM groups, which were approximately the same in average grade of staining. Inflammation of the superior bulbar conjunctiva, such as superior limbic keratitis, has been suggested as a possible source of symptoms in DE, particularly in highly symptomatic cases that show no other obvious ocular surface signs of DE.[54] Inflammation of the superior conjunctiva also occurs in CL wear and is known to be related to symtompatology.[55] Previous work by our group showed that greater superior decentration of a soft CL was significantly associated with increased VAS ratings of dryness[56]; however, in the current study, the CLIDE group showed very little superior conjunctival staining, significantly less than in the DE group.

Curiously, a significant intergroup difference was found in grade of lower lid blepharitis, with the highest average grade found in the ASYM group. Blepharitis has long been associated with ocular inflammation and dryness and other symptoms.[57] This counterintuitive result could be explained simply as being the result of sampling error or random chance. It is also possible to speculate that subjects in the DE and CLIDE groups, who are symptomatic yet manage to tolerate full-time CL wear, may be able to continue lens wear by frequently practicing eyelid hygiene, whereas ASYM subjects are sufficiently comfortable (perhaps due to desensitization or naturally lower pain sensitivity) to become lax in their attention to lens-wearing hygienic practices.

A second curious result in the current study was that the number of partial blinks during the 30-sec LipiView scan was fewest in the CLIDE group, most in the DE group, with the ASYM group averaging between the two. Although it makes sense intuitively to observe more partial blinks in the uncomfortable eyes of the DE group compared with the ASYM group, it is not clear why the CLIDE group would exhibit the fewest partial blinks. Yeh and Lin[58] recently reported that individuals who were recorded as having all partial blinks during the LipiView measurement period had, on average, a thicker tear lipid layer than those who were recorded as having at least one complete blink. A healthy lipid layer is considered to be at least 60 nm thick, although merely having sufficient quantity of lipid does not necessarily indicate a healthy lipid layer.[59] For example, individuals with hypersecretory Meibomian gland dysfunction or blepharitis can be symptomatic for DE even with a very thick lipid layer.[60] The complex relationships among the mechanisms of full versus partial blinking, symptomatology and the Meibomian glands and tear lipid layer warrant further study.

As with any study, there are limitations. First, it should be kept in mind that this study was conducted on and around the UCB campus with its attendant demographics, defined the study groups for analysis based on DEFC scores, and followed certain eligibility criteria. Broad generalizations to target populations substantially unlike our study population, or comparisons to other DE studies using different methods and criteria, should be undertaken with due caution. Second, sample sizes were relatively small, lowering our statistical power to detect other significant associations should any actually exist. It is possible that some marginal relationships between symptom group and other factors, such as ethnicity (P=0.061) or corneal staining (P=0.068), could actually be true in the population, but we lack the statistical power to detect the relationship with 95% confidence. Larger sample sizes and additional statistical power would also permit investigation of further refinements in differentiation based on causal or exacerbating factors, such as lens care systems that can affect symptoms both during and after lens wear.[61,62] A third item to bear in mind is that because of our study protocol in which subjects discontinued lens wear at least 24 hr before the visit, precorneal NITBUT was measured hours after lens removal. It is not known whether or not the distinction between CLIDE and DE in precorneal NITBUT would be apparent immediately after lens removal (e.g., at a patient visit to the eye doctor). Finally, the associations between symptom group and other factors presented in this article represent group average effects. Further study would be needed to evaluate diagnostic performance (e.g., sensitivity and specificity) and to determine optimum diagnostic thresholds before using these subjective response instruments and clinical measurements to diagnose and monitor individual patients in the clinical setting.

CONCLUSIONS

In this study, we have shown that (1) nearly half of symptomatic CL wearers have symptoms that are not directly CL-induced, (2) CL wearers with symptoms that resolve on lens removal present with similar symptomatology to those with underlying physiological DE, but (3) several clinical and laboratory assessments find those with CLIDE to be more similar to asymptomatic wearers, with worse outcomes only for those with underlying DE disease. In other words, broadly speaking, the ASYM and CLIDE groups show similar clinical signs, whereas the CLIDE and DE groups are more similar in symptom reporting. The clinician is recommended to determine symptomatology with lenses on and after lenses are removed and to assess the precorneal NITBUT, superior conjunctival staining, and anterior displacement of the upper eyelid Line of Marx. It is critical for clinicians and researchers both, once a CL wearer has presented with symptoms, to investigate further using a combination of questionnaire instruments, clinical assessments, and objective measurements, to determine the underlying causes or contributing factors, to achieve successful patient treatment and valid, generalizable clinical study results.

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