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The Association Between Mucin Balls and Corneal Infiltrative Events During Extended Contact Lens Wear

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Abstract

Purpose—This study determined the association between mucin ball formation and corneal infiltrative events (CIEs) during continuous wear (CW) with lotrafilcon A silicone hydrogel (SH) contact lenses.

Methods—Subjects (n=205) in the Longitudinal Analysis of Silicone Hydrogel Contact Lens Study wore lotrafilcon A contact lenses for 12 months of CW. The primary outcome was a CIE. Kaplan-Meier methods were used to estimate the unadjusted cumulative incidence of remaining CIE free stratified by mucin ball presence. Cox proportional hazards regression was used to model the hazard of developing a CIE as a function of mucin ball formation and other covariates.

Results—Over half (54.2%) of subjects displayed some presence of mucin balls during at least one visit and about one-third (32.8%) displayed repeated episodes. Mucin ball scores were correlated between the two eyes and weakly correlated with corneal curvature ($p<=0.005$). Univariate analyses revealed that the relative hazard for a CIE was 0.35 (95% confidence interval (CI) 0.19–0.68) if a single episode of mucin balls was detected and 0.17 (95% CI 0.06–0.43) if repeated episodes were detected. Upon multivariate analysis, repeated presence of mucin balls was associated with an 84% decreased hazard of experiencing a CIE (hazard ratio 0.16, 95% CI 0.06–0.44).

Conclusions—The presence of mucin balls is significantly associated with a decreased incidence of CIEs, and the effect is greatest when they are repeatedly present over time. We hypothesize that mucin ball presence represents a more concentrated or viscous mucus layer which prevents upregulation of the immune response against bacterial ligands.

INTRODUCTION

Mucin balls are spherical, translucent, insoluble, substantially rigid, tear film derived bodies composed of naturally occurring mucins on the ocular surface that form between the back surface of a contact lens and the corneal epithelium.[1–3] Upon removal of the contact lens, the mucin balls are rapidly blinked away, however, they leave behind depressions within the

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corneal epithelium. The depressions display unreversed illumination and are therefore visible with the slit-lamp biomicroscope, however, their appearance is enhanced with instillation of sodium fluorescein because fluorescein pools within the depressions.[1, 2, 4] After lens removal, the depressions completely resolve within 24 hours.[1, 4]

Confocal microscopy indicates that the sizes of mucin balls range from 34 μm to 79 μm.[3, 5] Their size is rather large in comparison to the post lens tear film whose thickness is about 1–2 μm,[6, 7] therefore, they become immobilized between the contact lens and corneal epithelium. The mucin ball induced depressions do not cause fluorescein to penetrate into the epithelium.[1, 2] However, because the corneal epithelium is about 50–70 μm, mucin balls can extend through the entire thickness of the corneal epithelium and reach the basal lamina.[3–5] They laterally displace epithelial cells rather than simply flatten them.[3]

The presence of mucin balls has been referred to as peculiar,[4] and a complication of lens wear.[8] Some have postulated that the gaps they form within the corneal epithelium may open a pathway for microorganisms to penetrate the cornea,[5] or they may represent a compromise of the mucus phase of the tear film.[7] One unpublished study reported that in subjects wearing daily wear lenses, the presence of mucin balls was associated with a greater risk of corneal infiltrative events (CIEs)[9], and others have recommended contact lens management strategies to reduce them.[1, 4] However, the presence of mucin balls does not impact visual acuity nor subject comfort or satisfaction,[1] and most studies assessing their presence have found no association with adverse ocular responses.[1, 10, 11] The presence of mucin balls has not shown any evidence of cellular infiltration by keratocytes or immune cells.[3] In fact, Morgan and Efron reported reduced conjunctival and limbal redness in the presence of mucin balls,[12] and they may simply reflect a specific, yet unknown, characteristic of mucins in the tear film.

Contact lenses made of SH materials are associated with a 2-fold increased risk of CIEs compared to their low Dk counterparts,[13, 14] but the etiology for this increased risk is unclear. The Longitudinal Analysis of Silicone Hydrogel (LASH) Contact Lens Study was designed to assess risk factors for the development of CIEs during CW with SH lenses. The conceptual model for CIE development is outlined in Figure 1. In this model, bacterial contamination of contact lenses is theorized to be a necessary but not sufficient risk factor for CIE development. The LASH Study confirmed that bacterial contamination of contact lenses is strongly associated with a CIE.[15] The LASH Study was also designed to assess the other variables in the conceptual model, that is, whether clinically evident changes to the superficial corneal epithelium in the form of corneal staining or mucin ball depressions were also associated. Corneal staining was not associated with development of a CIE over time.[15] The purpose of this report is to assess the association between mucin ball formation and development of CIEs.

METHODS

The LASH Study was a prospective cohort study of subjects fit to the Night & Day SH lens (lotrafilcon A, Ciba Vision, Duluth, GA) for up to 29 consecutive nights of CW, with monthly disposal, and followed for 1 year. The primary outcome was the time to development of a CIE. The study was approved by the University Hospitals Case Medical Center Institutional Review Board and followed all the Tenets of the Declaration of Helsinki. The purpose of this report is to determine the impact of mucin ball formation on the cumulative incidence of CIEs in the LASH Study.

The LASH Study cohort and design have been detailed elsewhere.[15, 16] In brief, healthy subjects were at least 15 years of age, with refractive errors between +6.00 Diopters (D) to

−10.00 D, minimal or no astigmatism, flat and steep keratometry readings between 39.00 D and 48.00 D, and no contraindications to CW lens use. Subjects returned for visits after 1 week of extended wear (EW), and then after 1, 4, 8 and 12 months of CW. At every visit, each eye was assessed for presence of a CIE using definitions adopted from the standards as listed in the "Institute for Eye Research/L.V. Prasad Eye Institute (IER/LVPEI) Guide To Corneal Infiltrative Conditions".[17] Additionally, a clinical severity matrix was used to gather signs and symptoms of a CIE which generated a cumulative CIE score per eye for each subject visit as reported previously.[15] Using these definitions, a subject was classified as experiencing a CIE if they had a visible presence of at least 1 corneal infiltrate of any size regardless of any other signs or symptoms, or if they had an incident corneal scar from a presumed contact lens peripheral ulcer during the follow-up period. Each visit also included an assessment of vision, lens fit, posterior lens debris, and front surface lens wetting and deposits. Lenses were aseptically removed and biomicroscopic evaluations were performed. Efron Grading Scales[18, 19] were used for grading blepharitis, meibomian gland dysfunction, corneal neovascularization, epithelial microcysts, and corneal edema. The IER grading scales[20] were used for grading upper tarsal plate redness and roughness, limbal redness, bulbar redness, conjunctival staining in 4 peripheral corneal zones, and corneal staining in 5 corneal zones. Sodium fluorescein was used to assess both corneal and conjunctival staining. The Schirmer test with anesthesia was performed at the 1 month CW visit. At selected visits, lenses were cultured using an agar overlay technique and the bioburden assessed as described previously.[16] Briefly, substantial bioburden was identified if a lens harbored pathogenic species or higher than normal levels of commensal species.

Grading of mucin balls was determined by quantifying the surface area and density of their fluorescein pooled depressions in each of 5 zones on the corneal surface. First, the presence of mucin balls was determined by the investigator by observation of the pearly grey microspheres trapped beneath the contact lens as seen through the slit lamp biomicroscope at each visit. If the investigator noted mucin ball presence, the location, quantity, and density of the mucin balls were recorded by observing their fluorescein pooled depressions after lens removal. Specifically, fluorescein strips were wet with one drop of saline prior to swabbing the inferior tarsal conjunctiva, and grading was performed with a yellow Wratten filter in combination with a cobalt blue filter over the light source. Surface area and density of the mucin ball depressions were recorded in each of 5 corneal zones using slightly modified versions of the IER grading scales[20] as shown in Figure 2.

The grading of mucin balls was also performed by masked readers using digitally acquired photographs using the same grading criteria as listed in Figure 2. Briefly, approximately 15 minutes after the investigator's staining evaluation, fluorescein was re-instilled using the same technique, and digital photographs were acquired using the Zeiss Photo-slit lamp and a modified version the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study's photographic slit-lamp protocol for corneal staining.[21] Up to 8 photographs were taken per eye at 16X magnification with the cobalt blue and Wratten filters in place at multiple focal planes to achieve various views of the fluorescein pooling pattern. Prior to grading images, each reader was trained and certified on the ability to grade corneal staining and to distinguish the brightly pooling, sharply bordered, round mucin ball depressions from corneal fluorescein uptake. Figure 3 displays two representative images to compare the differences between typical contact lens induced corneal staining and mucin ball induced fluorescein pooling.

For every eye at each visit, a score representing magnitude of mucin ball presence was derived for each of the 5 corneal zones and an overall score was calculated by adding up the scores of the individual zones. Possible scores ranged from 0 (no mucin ball presence) to 20 (extensive mucin ball presence in all 5 zones). Additionally, the overall degree of mucin ball

presence was defined as “any reportable presence” or “substantial presence” after consideration of surface area and density as listed in Table 1, and the frequency of each level was reported separately for investigator graded data and masked reader data. Once the eye with a CIE was determined, mucin ball variables were drawn from the eye with a CIE at visits preceding the event, or the left eye for event free subjects.

Mucin ball variables were stratified and modeled as binary fixed covariates as 1) present (or absent) on at least one visit preceding a CIE or any visit for event free subjects, and 2) repeatedly present (or not) on at least two visits preceding a CIE or any visits for event free subjects. Mucin ball variables were additionally modeled as time dependant covariates in separate analyses. Clinical, biomicroscopic, and demographic variables were stratified and modeled as binary fixed covariates as listed in Table 2.

Statistical Methods

Univariate analyses including chi-square tests, Fisher’s exact tests, and univariate logistic regressions were used to examine associations between mucin ball presence and substantial lens bioburden, subject demographics, and biomicroscopic findings. Spearman’s rank correlations of mucin ball scores and hours awake at the time of examination, flat keratometry readings, and between eyes were performed for each visit.

Time-to-event analyses were conducted with mucin ball presence as the primary covariate and time to CIE development as the outcome. A subject was classified as experiencing a CIE at the first occurrence of any CIE regardless of severity in either eye. If a subject had a bilateral first event, the eye with the more severe CIE was used. Once the eye with a CIE was determined, data were drawn from the eye that had the CIE at visits preceding the event, except lens microbiology which included data on the day of the event. If a subject ended the study event free, the covariates from the left eye were used in the analysis.

Kaplan-Meier (KM) methods were used to estimate the unadjusted cumulative incidence of remaining CIE free stratified by 1) presence or absence of at least one episode of mucin balls or 2) repeated episodes of any reportable mucin ball presence. KM methods were repeated for substantial mucin ball presence. The log-rank test was used to determine if there were significant differences in cumulative incidence of CIE by these variables. Univariate Cox proportional hazards regressions were used to determine initial assessments of risk for each level of mucin ball presence.

Potential confounding variables were assessed by determining if univariate associations existed between various demographic or clinical covariates of interest with both mucin ball presence and time to developing a CIE. Variables found to be significant in previous analyses[15], biologically plausible covariates, and potential confounders were examined in a multivariable Cox proportional hazards model. All analyses were conducted using SAS version 9.1.3 (SAS Institute, Inc., Cary, NC) procedures.

RESULTS

Across all 1047 subject-visits, about one-third displayed some degree of mucin balls and about one-tenth displayed substantial presence of mucin balls (Table 1). The ability to grade mucin ball presence was consistent between the masked readers and the investigator. The frequency of mucin ball presence by visit is displayed in Table 3. Although mucin balls appeared in about 30% of subjects by the 1 week visit, the percentage of subjects exhibiting mucin balls rose to about 50% at the 1 month visit and stayed relatively constant (or higher) thereafter. Across subjects, over half displayed at least one episode of reportable mucin ball presence and about one-third displayed repeated episodes (Table 4).

There was no correlation between the mucin ball score and the number of hours a subject was awake at any visit ($p>0.08$). Mucin ball scores were correlated between the two eyes at each visit as seen in Table 5. Lastly, there was a small correlation between mucin ball scores and flat keratometry readings at the 4 month visit (right eye $r=0.2544$, $p=0.0047$; left eye $r=0.2603$, $p=0.0036$).

The KM unadjusted cumulative incidence after 12 months of follow-up for development of a CIE of the entire cohort was 26.7% (95% CI 20.1–35.0%).[15] Specifically, there were 44 incident CIEs in 38 subjects (6 were bilateral events), 30 were symptomatic events and 14 were asymptomatic. There were no events of microbial keratitis. Table 4 lists the univariate associations between mucin ball presence and development of CIE. Highly significant protective associations were noted between mucin ball presence and CIE development regardless if mucin balls were present during at least one visit or on repeated visits. The associations between substantial mucin ball presence and CIE development were not as significant. The same trends were noted whether masked reader data or investigator data were used. Figure 4 displays the KM plot for time to developing a CIE stratified by presence or absence of at least a single episode of mucin ball formation. There is evidence for decreased cumulative incidence of CIEs in subjects with mucin balls, especially after about 120 days. Figure 5 displays the KM plot for time to developing a CIE stratified by presence or absence of repeated mucin ball formation. There is evidence for decreased cumulative incidence of CIEs in subjects with repeated episodes of mucin balls, which remained fairly consistent throughout the study period. When modeled as a time dependant covariate, no association between mucin balls and CIEs was detected.

Univariate associations between repeated mucin ball presence and other demographic and clinical covariates of interest are listed in Table 2. Significant associations (at $p<0.10$) were noted between repeated mucin ball presence and blepharitis, Asian race, frequent use of rewetting drops, and smoking. To determine if any of these significant covariates served as potential confounders between repeated mucin ball presence and CIEs, the associations between CIE development and these same covariates were assessed in previous analyses.[15] Neither blepharitis, Asian race, nor frequent use of rewetting drops were associated with a CIE. Smoking was previously noted to increase the risk for CIE by about 4-fold[15] thus, it was controlled for in the multivariate analysis. Bacterial bioburden, conjunctival stain, age, and gender were found to be important variables in CIE development[15] thus, they were also retained in the final multivariate model.

Table 6 presents the results of the multivariate analysis. Repeated presence of mucin balls was associated with an 84% decreased hazard of experiencing a CIE.

DISCUSSION

In the LASH Study, the presence of mucin balls was found to be a protective indicator of CIE development during CW with SH contact lenses. Specifically, subjects which formed mucin balls were found to have an 84% decreased hazard of CIE development. The detailed capture and grading of mucin ball indentations provided robust data to explore the hypothesis that the presence of mucin balls during SH lens CW is somehow related to CIE development. Contrary to our proposed hypothesis and conceptual model, subjects which produce mucin balls have a decreased risk for CIE development compared to those that do not.

Mucin balls were first described in 1988 and have been previously referred to as lipid plugs,[22] tear microspheres,[23] and microdeposits.[24] A subset of the population is predisposed to develop mucin balls irrespective of the lens material worn, but lens material influences

the degree of mucin ball formation.[25] Mucin balls have been shown to occur in greater number, and usually greater frequency, during SH lens wear compared to low oxygen permeable hydrogel lens wear.[3, 25] Longer periods of SH lens wear have also resulted in greater numbers of mucin balls trapped in the post-lens tear film.[1, 4, 11]

When initially named, mucin balls were only suspected to be composed of ocular mucins. In 2003, Millar provided the definitive evidence that mucin balls are indeed composed of collapsed ocular mucin with no evidence of lipid or bacterial encapsulation.[3] The mucus layer, present along the apical surface of the entire ocular surface epithelium, provides a barrier to pathogen penetrance, a mechanism for removal and trapping of particulates, and a means of hydrating the ocular surface.[26] Mucus is a colloid composed of mucins and inorganic salts suspended in water.[27] Mucins are strongly hydrophilic glycosylated proteins, which have strong barrier properties against microbial invasion and can also inhibit bacterial multiplication.[27, 28] At least 4 of the 19 human mucin genes are expressed by the ocular surface epithelium (MUC1, MUC4, MUC5, MUC16).[26, 29] MUC1, MUC4 and MUC16 are membrane spanning mucins; MUC1 and MUC16 are produced by all ocular surface epithelia including corneal epithelium and MUC4 is most prevalent in conjunctival epithelium.[26, 29, 30] MUC5AC is a secretory mucin derived from conjunctival goblet cells.[30] Secretory mucins form a highly hydrated gel over epithelial surfaces providing lubrication and protection.[31] The membrane spanning mucins constitute the glycocalyx atop the conjunctival and corneal epithelia which is covered by a mucous blanket composed of the secreted mucins.[27] Together, these mucins compose the posterior layer of the pre-ocular tear film, beneath the aqueous and lipid layers. Reports on potential alterations of mucin expression during contact lens wear are inconclusive. Although some groups report decreased expression of several mucins with contact lens wear[32–34], others report decreased mucin expression only in symptomatic wearers[35], and others have found no differences in mucin expression between lens wearers and non-wearers.[36]

Mucin balls are thought to occur as a result of shear and tension forces caused by the mechanical interaction of the lens with the ocular surface,[11] and they have been observed in all quadrants of the cornea.[1] The high modulus of SH lenses (especially the lotrafilcon A material),[37] coupled with minimal protein deposition[38] and depletion of aqueous tears beneath lenses during overnight wear,[39, 40] results in a mucin-rich post-lens tear film. The inherent surface tension forces associated with SH lens movement during blinking and rapid eye movement cause the viscous and concentrated mucin to roll up into spheres.[2, 7]

Tan and colleagues reported the incidence of mucin balls varied from about 50% to 82% across repeated visits of subjects wearing SH lenses for extended wear.[25] Dumbleton and others have reported 70% of subjects exhibit mucin balls with lotrafilcon A lens extended wear,[1, 12] 29% exhibit them repeatedly across study visits[1], and only about 5% demonstrate significant numbers.[8] The incidence of subjects exhibiting mucin balls in the LASH Study was about 54% for at least one episode of mucin ball formation and 18% for repeated episodes. The incidence in the LASH Study is slightly lower than others have reported previously. In Dumbleton's study[1], only adapted contact lens subjects already successful in extended wear were enrolled, whereas previously successful extended wear was not a prerequisite for the LASH Study. Therefore, if the ability to form mucin balls is protective, then perhaps Dumbleton's subjects had higher levels of mucin as a group (compared to the LASH cohort) which contributed to their success in extended wear at study entry and subsequently resulted in greater incidence of mucin ball formation.

Two other groups have also reported steeper corneal curvatures to be associated with greater mucin ball presence when only a single, relatively flat, base curve was used.[1, 25] Dumbleton and colleagues postulated that a greater "mismatch" between the lens and corneal surface

results in more lens movement and mucin ball formation presumably from greater shear friction forces incurred with movement. In the LASH Study, two base curves were used, and the majority of subjects were fit with the 8.4 mm base curve lens. Thus, presumably the effect of a "mismatched" lens to cornea fitting relationship was lessened in the LASH Study which could have accounted in a lower incidence; nonetheless, the incidence was still considerably high and the correlation with steeper corneal curvatures remained.

There was sufficient rationale to consider the impact of mucin ball formation on CIE development. Ladage has shown that mucin ball indentations can reach the basal lamina, and Ki-67 positive stromal cells were detected beneath these deep depressions indicating active proliferation and a focal increase in stromal cell density.[5] Fleiszig has demonstrated that the mucus phase is critically important in preventing attachment of potential pathogens to the corneal surface.[41, 42] In the absence of a properly formed mucus layer, bacteria are more likely to attach to the cornea and establish infection,[7] or initiate an inflammatory response. Approximately, one third of SH lenses harbor substantial lens bioburden during CW.[16] If the protective mucus layer is disrupted in any way, the prevalent bacterial presence on lens surfaces may upregulate the immune response and result in a CIE.

On the contrary, the presence of mucin balls, especially in a repeated fashion, is significantly associated with a decreased incidence of CIEs. The mucin balls themselves are not likely protective, although they may entrap foreign objects or microbes which can halt an immune response against such ligands, or they may act like a "ball bearing" to separate the lens physically from the corneal epithelium. A more plausible explanation is that subjects who produce mucin balls have specific mucin characteristics rendering them less likely to develop signs of corneal inflammation. Indeed, our findings (lack of an association in the time dependant analysis) argue that the protective effect likely reflects a chronic rather than an acute factor. One theory is that mucin balls may be a biomarker for a more concentrated or viscous mucus layer.

Silicone hydrogel lens wear probably results in the formation of more mucin balls because they adsorb many fewer proteins and mucins compared to their hydrogel counterparts.[38, 43] Conventional hydrophilic materials deposit both membrane spanning and secretory ocular surface mucins[44] into the lens matrix which masks their post-lens tear film presence. The lower deposition of SH materials coupled with the higher modulus of the material mechanically rolls up the mucins making them visible. The effect is greatest with SH lenses of high modulus, and thus we have easily captured their presence with use of the lotrafilcon A material which has the highest modulus of any SH lens type. Results would likely differ if other SH lenses of lower modulus were used. The differences between subjects that display mucin balls with lotrafilcon A lenses and those that do not may simply reflect differences in their mucin characteristics.

Differential diagnoses which can lead to exposure misclassification include filamentary keratitis, microcysts, vacuoles, and dimple veils from trapped air bubbles.[1, 4] Mucin balls differ from corneal filaments which are prevalent in ocular surface disease and are composed of damaged cells and mucins that form long strands which are adherent to damaged sites on the corneal surface.[45] No LASH Study subjects had filamentary keratitis, thus, it is not likely that filaments were misclassified as mucin balls. Although microcysts, vacuoles, and dimple veils can resemble mucin balls, it is not likely that they mimicked the appearance of mucin ball indentations in this study. Corneal epithelial microcysts consist of necrotic cellular tissue or cellular debris secondary to hypoxia. They are typically smaller than mucin balls, less commonly found with longer term wear of SH lenses, and they do not induce surface depressions which pool with fluorescein.[1, 4] Vacuoles are also an epithelial response to hypoxia, and although they appear perfectly round as mucin balls do, they do not

create depressions nor pool fluorescein. Lastly, trapped air bubbles can create indentations that pool fluorescein (dimple veils), but the air bubbles would have been clearly visible on biomicroscopic evaluation before lens removal. Thus, the technique used in the LASH Study to identify mucin ball presence (fluorescein pooling of indentations) is probably the best method to avoid exposure misclassification.

The theory generated from this study is that mucin balls reflect a mucin rich tear film which is protective against microbial stimulation of the immune system. In other words, the clinical observation of mucin balls, especially when present repeatedly, but regardless of number or density, indirectly reflect a subject who is relatively "protected against" a CIE. Microbes present on lens surfaces will become enveloped in, or physically cannot penetrate the mucus-rich tear film and thus will be unable to upregulate the immune response at the epithelial surface. Further research is required in this area to confirm this theory and better understand the role mucins play in contact-lens-associated infiltrative keratitis.

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References

1. Dumbleton K, Jones L, Chalmers R, Williams-Lyn D, Fonn D. Clinical characterization of spherical post-lens debris associated with lotrafilcon high-Dk silicone lenses. CLAO J. 2000; 26:186–92. [PubMed: 11071342]
2. Pritchard N, Jones L, Dumbleton K, Fonn D. Epithelial inclusions in association with mucin ball development in high-oxygen permeability hydrogel lenses. Optom Vis Sci. 2000; 77:68–72. [PubMed: 10701804]
3. Millar TJ, Papas EB, Ozkan J, Jalbert I, Ball M. Clinical appearance and microscopic analysis of mucin balls associated with contact lens wear. Cornea. 2003; 22:740–5. [PubMed: 14576525]
4. Craig JP, Sherwin T, Grupcheva CN, McGhee CN. An evaluation of mucin balls associated with high-DK silicone-hydrogel contact lens wear. Adv Exp Med Biol. 2002; 506:917–23. [PubMed: 12614010]
5. Ladage PM, Petroll WM, Jester JV, Fisher S, Bergmanson JP, Cavanagh HD. Spherical indentations of human and rabbit corneal epithelium following extended contact lens wear. CLAO J. 2002; 28:177–80. [PubMed: 12394542]
6. Nichols JJ, King-Smith PE. The effect of eye closure on the post-lens tear film thickness during silicone hydrogel contact lens wear. Cornea. 2003; 22:539–44. [PubMed: 12883347]
7. Efron N. Contact lens-induced changes in the anterior eye as observed in vivo with the confocal microscope. Prog Retin Eye Res. 2007; 26:398–436. [PubMed: 17498998]
8. Dumbleton K. Noninflammatory silicone hydrogel contact lens complications. Eye Contact Lens. 2003; 29:S186–9. discussion S90–1, S92–4. [PubMed: 12772763]
9. Carnt NKL, Naduvlath T, Holden B, Willcox M. Risk Factors Associated with Corneal Inflammation in Soft Contact Lens Daily Wear. ARVO. 2007:E-abstract 4326.
10. Sweeney, DF.; du Toit, R.; Keay, L.; Jalbert, I.; Sankaridurg, P.; Stern, J.; Skotinsky, C.; Stephensen, A.; Covey, M.; Holden, B.; Rao, G. Clinical Performance of Silicone Hydrogel Lenses. In: Sweeney, DF., editor. Silicone Hydrogels Continuous Wear Contact Lenses. Edinburgh: Butterworth-Heinemann; 2004. p. 164-216.

11. Stern J, Wong R, Naduvilath TJ, Stretton S, Holden BA, Sweeney DF. Comparison of the performance of 6- or 30-night extended wear schedules with silicone hydrogel lenses over 3 years. Optom Vis Sci. 2004; 81:398–406. [PubMed: 15201712]
12. Morgan PB, Efron N. Comparative clinical performance of two silicone hydrogel contact lenses for continuous wear. Clin Exp Optom. 2002; 85:183–92. [PubMed: 12033981]
13. Radford CF, Minassian D, Dart JK, Stapleton F, Verma S. Risk factors for nonulcerative contact lens complications in an ophthalmic accident and emergency department: a case-control study. Ophthalmology. 2009; 116:385–92. [PubMed: 19167088]
14. Szczotka-Flynn L, Diaz M. Risk of corneal inflammatory events with silicone hydrogel and low dk hydrogel extended contact lens wear: a meta-analysis. Optom Vis Sci. 2007; 84:247–56. [PubMed: 17435508]
15. Szczotka-Flynn L, Lass J, Sethi A, Debanne S, Benetz B, Albright M, Gillespie B, Kuo J, Jacobs M, Rimm A. Risk Factors for Corneal Infiltrative Events During Continuous Wear of Silicone Hydrogel Contact Lenses. Invest Ophthalmol Vis Sci. 2010 Jun 10. [EPub ahead of print].
16. Szczotka-Flynn LB, Bajaksouzian S, Jacobs MR, Rimm A. Risk factors for contact lens bacterial contamination during continuous wear. Optom Vis Sci. 2009; 86:1216–26. [PubMed: 19786927]
17. Institute for Eye Research. [9/25/09] Institute for Eye Research (IER)/LVPEI Guide to Corneal Infiltrative Conditions. Available at: http://www.siliconehydrogels.org/resources/index.asp. Accessed
18. Efron, N. Grading scales for contact lens complications. Appendix A. In: Efron, N., editor. Au Contact Lens Complications. 2. 2004. p. 239-43.
19. Efron NMP, Katsara SS. Validation of grading scales for contact lens complications. Ophthal Physiol Opt. 2001; 21:17–29.
20. Institutefor Eye Research. [9/25/09] Institute for Eye Research Grading Scales. Available at: http://www.siliconehydrogels.org/resources/index.asp. Accessed
21. Barr JT, Schechtman KB, Fink BA, Pierce GE, Pensyl CD, Zadnik K, Gordon MO. Corneal scarring in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study: baseline prevalence and repeatability of detection. Cornea. 1999; 18:34–46. [PubMed: 9894935]
22. Fleming C, Austen R, Davies S. Pre-corneal deposits during soft contact lens wear. Optom Vis Sci. 1994; 71:S152–3.
23. Tan J, Keay L, Jalbert I, et al. Tear microspheres (TMSS) with high Dk lenses. Optom Vis Sci. 1999; 76:226.
24. Bourassa SBW. Transient corneal surface “microdeposits” and associated epithelial surface pits occurring with gel contact lenses extended wear. Int Contact Lens Clin. 1988; 15:338–40.
25. Tan J, Keay L, Jalbert I, Naduvilath TJ, Sweeney DF, Holden BA. Mucin balls with wear of conventional and silicone hydrogel contact lenses. Optom Vis Sci. 2003; 80:291–7. [PubMed: 12692485]
26. Danjo Y, Hazlett LD, Gipson IK. C57BL/6 mice lacking Muc1 show no ocular surface phenotype. Invest Ophthalmol Vis Sci. 2000; 41:4080–4. [PubMed: 11095599]
27. Ramamoorthy P, Nichols JJ. Mucins in contact lens wear and dry eye conditions. Optom Vis Sci. 2008; 85:631–42. [PubMed: 18677222]
28. Berry M, Harris A, Lumb R, Powell K. Commensal ocular bacteria degrade mucins. Br J Ophthalmol. 2002; 86:1412–6. [PubMed: 12446377]
29. Blalock TD, Spurr-Michaud SJ, Tisdale AS, Gipson IK. Release of membrane-associated mucins from ocular surface epithelia. Invest Ophthalmol Vis Sci. 2008; 49:1864–71. [PubMed: 18436821]
30. Mantelli F, Argueso P. Functions of ocular surface mucins in health and disease. Curr Opin Allergy Clin Immunol. 2008; 8:477–83. [PubMed: 18769205]
31. Kardon R, Price RE, Julian J, Lagow E, Tseng SC, Gendler SJ, Carson DD. Bacterial conjunctivitis in Muc1 null mice. Invest Ophthalmol Vis Sci. 1999; 40:1328–35. [PubMed: 10359313]
32. Corrales RM, Galarreta D, Herreras JM, Saez V, Arranz I, Gonzalez MJ, Mayo A, Calonge M, Chaves FJ. Conjunctival mucin mRNA expression in contact lens wear. Optom Vis Sci. 2009; 86:1051–8. [PubMed: 19661836]

33. Pisella PJ, Malet F, Lejeune S, Brignole F, Debbasch C, Bara J, Rat P, Colin J, Baudouin C. Ocular surface changes induced by contact lens wear. Cornea. 2001; 20:820–5. [PubMed: 11685059]
34. Yasueda S, Yamakawa K, Nakanishi Y, Kinoshita M, Kakehi K. Decreased mucin concentrations in tear fluids of contact lens wearers. J Pharm Biomed Anal. 2005; 39:187–95. [PubMed: 16085139]
35. Berry M, Pult H, Purslow C, Murphy PJ. Mucins and ocular signs in symptomatic and asymptomatic contact lens wear. Optom Vis Sci. 2008; 85:E930–8. [PubMed: 18832968]
36. Hori Y, Argueso P, Spurr-Michaud S, Gipson IK. Mucins and contact lens wear. Cornea. 2006; 25:176–81. [PubMed: 16371777]
37. Tighe, B. Silicone Hydrogels: the Rebirth of Extened Wear Contact Lenses. Oxford: Butterworth Heinemann; 2000. Silicone Hydrogel Materials: How do they Work? In: Sweeney DF, editor; p. 1-21.
38. Green-Church KB, Nichols JJ. Mass spectrometry-based proteomic analyses of contact lens deposition. Mol Vis. 2008; 14:291–7. [PubMed: 18334948]
39. Bruce AS, Brennan N. Hydrogel Lens Binding and the Postlens Tear Film. Clin Eye Vis Care. 1992; 4:111–6.
40. Bruce AS, Mainstone JC. Lens adherence and postlens tear film changes in closed-eye wear of hydrogel lenses. Optom Vis Sci. 1996; 73:28–34. [PubMed: 8867679]
41. Fleiszig SM, Zaidi TS, Pier GB. Mucus and Pseudomonas aeruginosa adherence to the cornea. Adv Exp Med Biol. 1994; 350:359–62. [PubMed: 8030502]
42. Fleiszig SM, Zaidi TS, Ramphal R, Pier GB. Modulation of Pseudomonas aeruginosa adherence to the corneal surface by mucus. Infect Immun. 1994; 62:1799–804. [PubMed: 8168942]
43. Boone A, Heynen M, Joyce E, Varikooty J, Jones L. Ex Vivo Protein Deposition on Bi-Weekly Silicone Hydrogel Contact Lenses. Optom Vis Sci. 2009
44. Berry M, Harris A, Corfield AP. Patterns of mucin adherence to contact lenses. Invest Ophthalmol Vis Sci. 2003; 44:567–72. [PubMed: 12556384]
45. Tanioka H, Yokoi N, Komuro A, Shimamoto T, Kawasaki S, Matsuda A, Kinoshita S. Investigation of the corneal filament in filamentary keratitis. Invest Ophthalmol Vis Sci. 2009; 50:3696–702. [PubMed: 19443713]

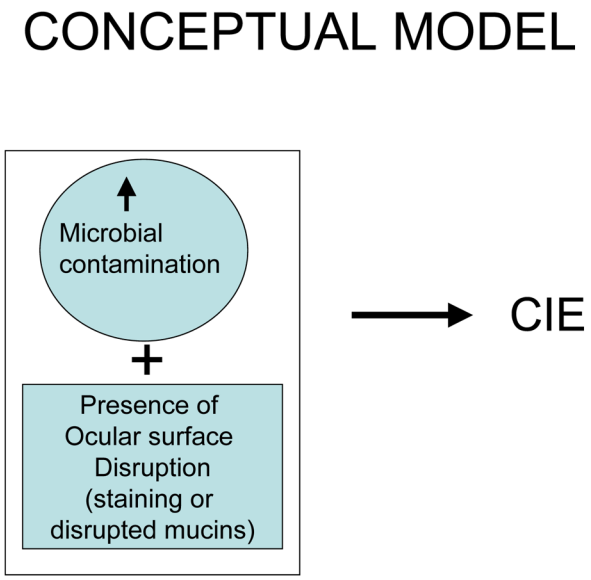

Figure 1.
Conceptual model for CIE development.

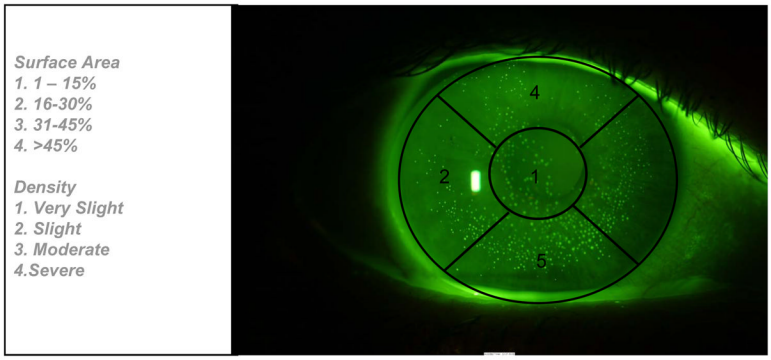

Figure 2.

Example of photographic mucin ball fluorescein depression grading. Each of the 5 corneal zones was graded for surface area and density of mucin ball depressions. On this subject-visit this eye was classified with substantial mucin ball presence.

Figure 3a

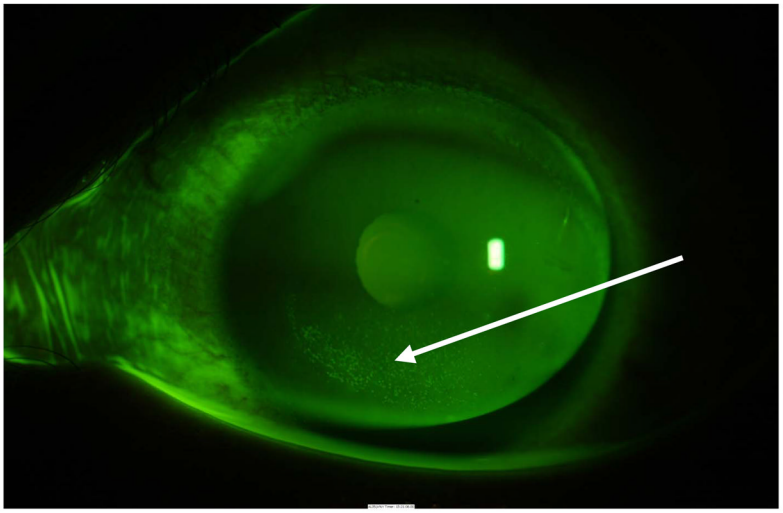

Figure 3b

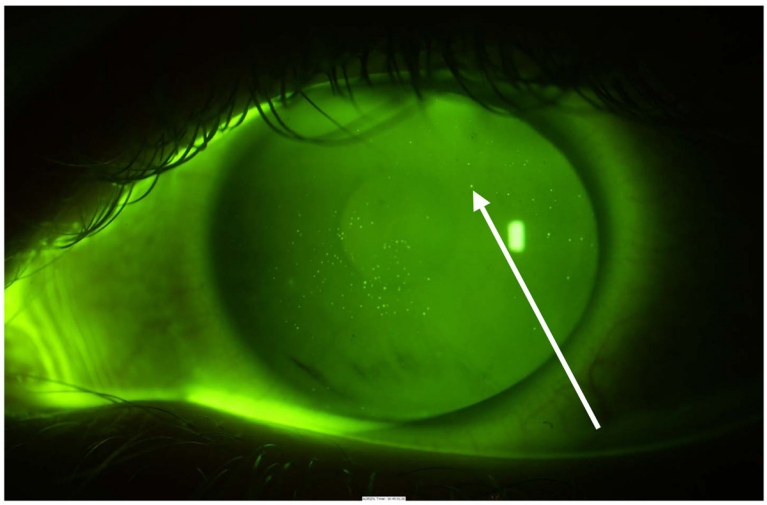

Figure 3.
Example of photographic differences between corneal staining and mucin ball fluorescein pooling depressions: a) arrow points to center of corneal fluorescein staining area displaying small and irregularly bordered dots of stain; b) arrow points to one of many mucin ball depressions pooling with fluorescein which are brighter, rounder, and larger than that noted in 2a.

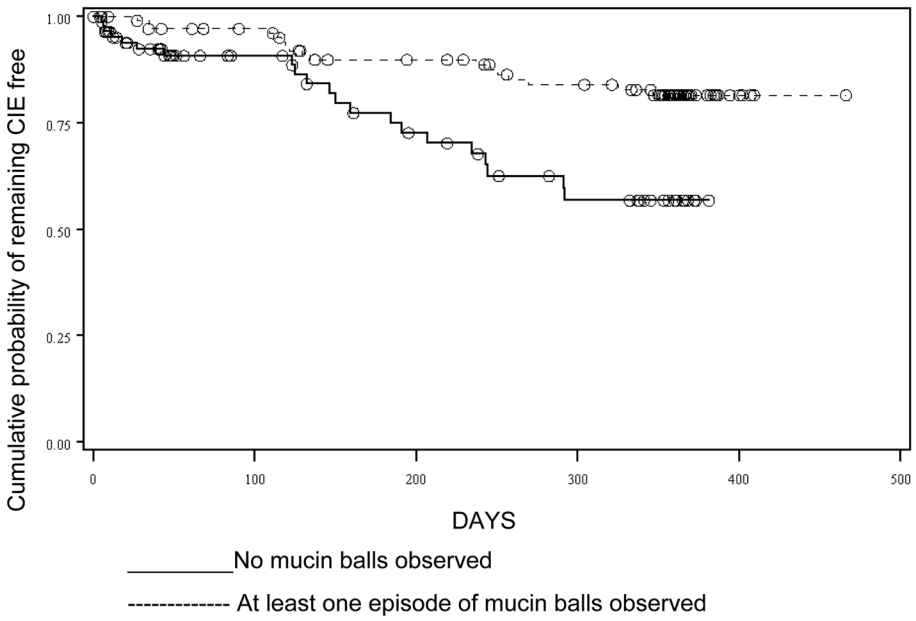

Figure 4.
Unadjusted cumulative probability of remaining CIE free stratified by presence or absence of at least one episode of mucin ball formation.

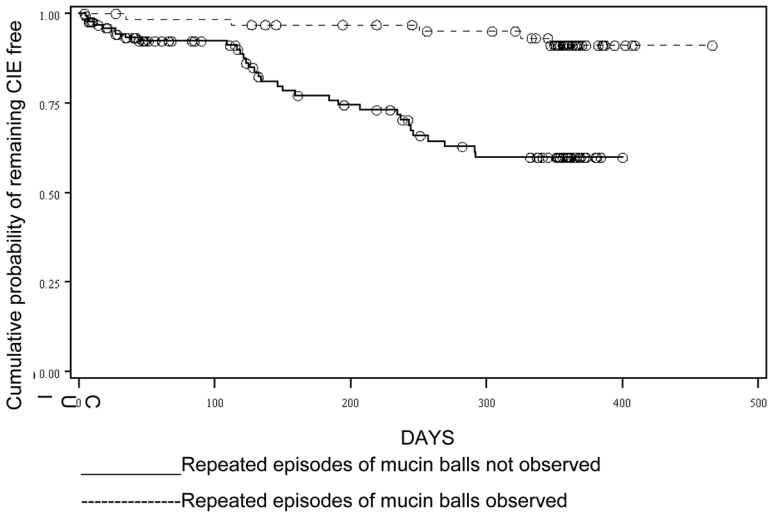

Figure 5.
Unadjusted cumulative probability of remaining CIE free stratified by presence or absence of repeated episodes of mucin ball formation.

TABLE 1

Grading of Mucin Ball Presence by Fluorescein Evaluation and Frequency of Occurrence Across 1047 subject-visits in LASH cohort

	Any reportable presence			Substantial Presence		
	#zones	**Surface Area**	**Density**	**#zones**	**Surface Area**	**Density**
	>=1	>=1	>=1	>3	>=1	>=1
				>=1	>=1	4
				>=1	4	>=1
				>=1	>2	>3
Frequency of subject-visits*†	34.8%			12.6%		
Frequency of subject-visits*‡	29.8%			10.0%		

† masked reader grading;

‡ investigator grading

Table 2

Stratification and Frequency of Demographic or Clinical Covariates and Univariate Logistic Regression Results for Presence of Repeatable Episodes of Mucin Ball Formation

Covariate	Frequency (%)	P value	Odds Ratio (95% Confidence Interval)
Baseline Covariates			
Current Smoker	21 (10.5%)	**0.0594**	0.31 (0.09–1.12)
Age; under 21	26 (12.7%)	0.7169	1.18 (0.49–2.83)
Male	48 (23.4%)	0.2505	0.67 (0.34–1.32)
Asian race	31 (15.1%)	**0.0309**	0.34 (0.13–0.94)
Neophyte	53 (25.9%)	0.7896	0.91 (0.45–1.83)
History of previous adverse event	90 (49.2%)	0.5626	1.21 (0.64–2.27)
Contact Lens Rx: greater than +−5.00D	63 (30.9%)	0.3827	0.76 (0.39–1.44)
Clinical Covariates			
Blepharitis; grade 2 or higher	20 (9.8%)	**0.0433**	2.51 (1.01–6.27)
Meibomianitis; grade 1 or higher	17 (8.3%)	0.1907	1.94 (0.71–5.28)
Upper palpebral conjunctival roughness; grade 2 or higher	95 (46.3%)	0.9563	0.98 (0.54–1.79)
Conjunctival Stain; grade 2 or higher	76 (37.1%)	0.2887	1.39 (0.76–2.56)
Bulbar Conjunctival Redness; grade 2 or higher	35 (17.1%)	0.8465	0.92 (0.42–2.03)
Limbal Redness; grade 2 or higher	36 (17.6%)	0.2684	0.63 (0.28–1.43)
Corneal Neovascularization; grade 1 or higher	20 (9.8%)	0.1974	0.47 (0.15–1.49)
Corneal Edema; grade 1 or higher	7 (3.4%)	0.2875	0.33 (0.04–2.81)
Dry Eye; <10mm wet on Schirmer strip	21 (12.4)	0.5863	1.35 (0.46–3.99)
Other Covariates			
Frequent use of rewetting drops	109 (55.6%)	**0.0558**	1.83 (0.98–3.39)
Substantial Lens Bioburden	60 (32.4%)	0.6820	0.87 (0.46–1.66)

Bold: significant at $p<0.10$

TABLE 3

Frequency of Mucin Ball Presence by Visit*

	1 week EW Visit	1 month CW visit	4 month CW visit	8 month CW visit	12 month CW visit
	n=180	***n=159***	***n=121***	**n=94**	**n=85**
Any mucin ball presence	26 (31.1%)	80 (50.3%)	75 (62.0%)	48 (51.1%)	48 (56.5%)
Substantial mucin ball presence	16 (8.9%)	24 (15.1%)	33 (27.5%)	19 (20.2%)	14 (23.5%)

* masked reader data

TABLE 4

Frequency and Repeatability of Mucin Ball Presence Across Subjects and Univariate Associations with CIE

	Masked Reader Grading			Investigator Grading		
	Frequency	**Hazard Ratio (95% Confidence Interval)**	**Log Rank Test P value**	**Frequency**	**Hazard Ratio (95% Confidence Interval)**	**Log Rank Test P value**
At least one episode of reportable mucin balls †	54.2%	0.35 (0.19–0.68)	0.0010	50.7%	0.189 (0.094–0.380)	<0.0001
At least one episode of substantial mucin balls †	18.1%	0.36 (0.13–1.03)	0.0463	18.1%	0.41 (0.16–1.06)	0.0582
Repeated episodes of reportable mucin balls *	32.8%	0.17 (0.06–0.43)	<0.0001	33.3%	0.16 (0.06–0.42)	<0.0001
Repeated episodes of substantial mucin balls *	10.8%	0.31 (0.07–1.29)	0.0878	7.7%	0.46 (0.11–1.93)	0.2787

† of 205 subjects

* of 195 subjects

Table 5

Correlations Between the Eyes for Mucin Ball Scores Across Visits

	1 month visit	4 month visit	8 month visit	12 month visit
r value	0.5030	0.6127	0.5995	0.6057
P value	<0.0001	<0.0001	<0.0001	<0.001

Table 6

Multivariate Analysis for Development of CIE

Variable	P value	Hazard Ratio	95% confidence interval
Repeated Mucin Ball Presence			
No	Referent		
Yes	0.0003	0.16	0.06–0.44
Substantial Lens Bioburden			
No	Referent		
Yes	<0.0001	4.45	2.11–9.39
Smoking			
Not currently	Referent		
Currently	0.0122	3.10	1.28–7.49
Conjunctival Stain			
No	Referent		
Yes	0.1406	0.56	0.26–1.21
Gender			
Female	Referent		
Male	0.2541	0.62	0.28–1.40
Age			
Over 21	Referent		
21 or younger	0.5752	1.29	0.53–3.15