Cornea

Mixed Model Analysis of Between-Subject Variability in Overnight Corneal Swelling and Deswelling With Silicone Hydrogel Lenses

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Purpose. To model between subject variability of corneal swelling (CS) and deswelling after overnight wear of silicone hydrogel (SiHy) contact lenses.

Methods. A total of 29 neophyte subjects wore 12 SiHy lenses with central transmissibility range of 31 to 211 Dk/t units on separate nights, in random order, and on one eye only. The contralateral eye served as the control. Central corneal thickness was measured using digital optical pachymetry before lens insertion, immediately after lens removal on waking, then 20, 40 minutes, 1, 2, and 3 hours later. Mixed modelling was conducted for simultaneous analysis of group and between-subject effects of CS and deswelling.

Results. The best model for overnight CS versus Dk/t was linear with a random intercept showing constant between-subject differences in CS for different Dk/t values. The best fit for corneal deswelling versus time was a curvilinear random intercept and random slope model. About 90% of the total between-subject deswelling variance in either lens or control eyes was due to the intercept variability with much less (~10%) being due to the variability of the individual deswelling rate (slope). Subject age, sex, and ametropia were not predictors of individual corneal swelling in the swelling versus Dk/t analysis. Age, however, was a significant (inverse) predictor of the rate of corneal deswelling, only in lens-wearing eyes.

Conclusions. A large proportion of variability in corneal swelling is because of subject-specific differences in corneal response to hypoxia. This shows that “low swellers” and “high swellers” actually do exist.

Keywords: corneal swelling, corneal deswelling, between-subject variability, pachymetry, mixed modeling

Corneal swelling is regarded as one of the main indices of corneal physiologic change as a result of corneal oxygen deficiency produced by contact lens (CL) wear.1,2 The postlens tear oxygen tension in soft lenses is dependent on the oxygen diffusion through the lens material3-4 and the effect of the tear pump on tear mixing to equilibrate the oxygen tension under a soft lens is insignificant.5,6 Therefore, oxygen diffusion through contact lenses plays a vital role in maintaining corneal health and normal physiology in soft lens wear.7,8 Corneal oxygen deprivation may lead to corneal swelling (thickening) from water absorption by the corneal stroma. This is believed to be due to the increased stromal osmotic gradient resulting from the accumulation of lactic acid from anaerobic metabolism in the cornea.9 It would appear self-evident, therefore, that the level of lens induced corneal swelling is inversely related to the oxygen transmissibility of the contact lens.10

The average overnight corneal swelling of 3%-4% occurs in response to eye closure11 in nonlens wearers12-15 and sleeping with a contact lens on the eye, further deprives the cornea of the oxygen supply from the palpebral vasculature, maximizing the hypoxic stress and potentially leading to increased corneal edema.16 Even silicone hydrogel (SiHy) lenses with high oxygen transmissibility do not limit the overnight corneal swelling to the level of no lens wear17 and so some subjects may reach potentially unsafe levels of overnight corneal swelling while wearing these highly oxygen permeable lenses.18

Lens attributes have been the primary focus of experiments examining the interactions between lens wear and corneal swelling. There is another aspect of the response to lenses, and that is the variability between subjects wearing the lenses. This has, in our opinion, been neglected. Two studies have specifically focused on intersubject/between-subject variability in corneal swelling,19,20 but it has been mentioned in others.19,21,22 It appears that the between-subject variability in corneal swelling is not dependent on lens oxygen transmissibility (Dk/t) because there is a similarly wide range of swelling response while wearing SiHy lenses18 and, interestingly, has been demonstrated with anoxia in the absence of any CL wear.19 These findings suggest that differences in the amount of corneal swelling between individuals (with similar oxygen supply) can be attributed to individual differences in corneal physiologic response to hypoxia (a random effect of subject) rather than the CL wear itself.
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Perhaps the absence of a direct examination of the role of subject variability in the many experiments examining corneal swelling during lens wear is a statistical one. Generally, in previous reports of corneal swelling, an averaging approach such as the “classical” repeated measures Analysis of Variance (Re-ANOVA) or regression analysis has been used.\textsuperscript{10,13,17,23–25} This approach compares group mean outcomes as fixed effects and is mathematically unable to address the structure of the underlying subject variability (i.e., the random effects or the individual specific responses). This random structure of corneal swelling or deswelling has never been reported. In our experiment, we conducted a “standard” corneal swelling experiment: Corneal thickness was measured with and without, and before and after overnight lens wear to examine swelling response and its recovery. The novel aspect of our report is to NOT be limited in what we are able to analyze about our predictor variables by only using averages: This is the first report about simultaneously controlling for both fixed (average) and random (subject) effects in SiHy lens induced overnight corneal swelling (CS) and deswelling analyses compared to no lens wear in the contralateral eye. We therefore took a ‘traditional’ experimental/analytical route to assess overnight corneal swelling when wearing contact lenses.\textsuperscript{25} However, the current study was also designed to measure the magnitude of the between-subject variability of CS and the magnitude of between-subject variability in deswelling after lens removal. In addition, we attempted to examine the association of between-subject variability of CS itself (intercept of the deswelling over time regression) and the individual recovery (variability in the slope of the recovery). Analysis of the whole range of CS and deswelling using this statistical approach can provide evidence for the presence of people in the sample who might be clinically referred to as “high-” and “low-swellers”, and also whether the course of recovery (within the study 3-hour limit) in high-swellers is the same or different than low-swellers. We also simultaneously examined the influence of the independent variables of age, sex, and the refractive error (auto-refraction spherical equivalent) in addition to the lens related independent variable of Dk/t on corneal swelling and deswelling over the 3-hour period after eye opening and lens removal. Explicitly then, the primary purpose of this study was to model the random structure of overnight central corneal swelling while wearing or not wearing SiHy contact lenses as well as deswelling after lens removal. We analyzed central corneal swelling as an index of corneal swelling response in overnight wear as maximum corneal swelling in closed-eye conditions expected to occur at the corneal center.\textsuperscript{25}

**Materials and Methods**

This was a double-masked study and all lenses were worn in random order and on a randomly determined eye (each decided with randomization tables established before the experiment was begun). The study was performed in compliance with the tenets of the Declaration of Helsinki. The study received ethics clearance through the Office of Research Ethics (ORE) at the University of Waterloo. Informed consent was obtained from all subjects prior to enrolment in the study.

**Subjects**

Based on previous data,\textsuperscript{17,24} 26 subjects were required to detect an 0.8% ± 1.2% difference in central corneal swelling with a power of 0.90 at α = 0.05. In this study 37 neophytes were enrolled and 29 completed the study (14 female, 15 male). The mean age of the subjects was 27.1 ± 7.9 years (median: 25 years; range: 17–50 years). Eight subjects chose to discontinue their participation in the study for nonlens related, personal reasons (relocation, finding a new job, etc.) before completing all follow-up visits: There is no reason to suppose that these participants would have added anything different to the data set. Only the data from the subjects who completed all study visits were included for data analysis. Table 1 summarizes the refractive characteristics of the subjects.

**Contact Lenses**

We used 4 SiHy lenses with 3 powers to change the Dk/t within each lens type. These 12 SiHy lenses and their nominal parameters are listed in Table 2. Central lens oxygen transmissibility (Dk/t) values were calculated using central lens thickness measurements and the manufacturers’ quoted lens permeability (Dk) values in the following formula:

\[
\frac{\text{Central Dk}}{t} = \frac{\text{Oxygen Permeability} \left( \frac{\text{cm}^2}{\text{s} \times \text{mm Hg}} \right)}{\text{Central Lens Thickness} \left( \text{cm} \right)}
\]

Giving units for Dk/t of \(\frac{\text{cm} \times \text{mlO}_{2}}{\text{ml s mm Hg}}\).

The central thickness and calculated Dk/t values that are presented in Table 3 were used as the lens transmissibility values in our analysis.

**Instruments**

Corneal thickness of each eye was measured using a digital optical pachometer mounted on a biomicroscope (Zeiss 30 SL-M; Carl Zeiss Meditec AG, Oberkochen, Germany). To enhance precision of the corneal thickness measurement at each time point, seven consecutive measurements were taken and the highest and the lowest readings were trimmed by the instrument’s custom software. The average of the remaining five measures was the recorded value of the corneal thickness provided that the standard deviation of these five measurements did not exceed 5 \(\mu\text{m}\), otherwise the measurement of that time point was repeated. The pachometer was calibrated at the beginning of the study using a method described elsewhere,\textsuperscript{26} and its calibration was verified and maintained throughout the study period.

Corneal swelling was defined as the percent of the difference in corneal thickness relative to baseline using the following formula:

\[
\% \text{corneal swelling} = 100 \left( \frac{\text{measured corneal thickness} - \text{baseline corneal thickness}}{\text{baseline corneal thickness}} \right)
\]

This is also how we defined the following terms throughout the paper:

**Table 1. Subject Refractive Characteristics**

<table>
<thead>
<tr>
<th>OD</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>K-readings</td>
<td></td>
</tr>
<tr>
<td>Flat K</td>
<td>42.94 ± 1.42</td>
</tr>
<tr>
<td>Steep K</td>
<td>43.44 ± 1.63</td>
</tr>
<tr>
<td>Corneal cylinder</td>
<td>−0.89 ± 0.42</td>
</tr>
<tr>
<td>Refractive error</td>
<td></td>
</tr>
<tr>
<td>Sphere</td>
<td>−0.29 ± 1.32</td>
</tr>
<tr>
<td>Cylinder</td>
<td>−0.38 ± 0.41</td>
</tr>
</tbody>
</table>

Measured as mean dipters (D) ± SD.
Corneal swelling (CS): increase in corneal thickness that was measured on eye opening in the morning (time = 0.0 hours)
Corneal deswelling: reduction in corneal thickness over the 3-hour period after lens removal (the function relating corneal swelling to time after eye-opening).

Procedures
Baseline corneal thickness (both eyes) was measured before lens insertion at each overnight visit. One of the randomly assigned study lenses was placed on the randomly predetermined eye, prior to sleep at 11 PM. Subjects were then carefully examined to ensure that the lenses were fitting properly, that there was no debris trapped between the lens and the cornea and that the lens was comfortable. The following morning subjects were woken at 7 AM to remove the lens. Immediately after removal, subjects were escorted to the exam room with their eyes closed. After the subjects were comfortably seated at the pachometer corneal thickness of each eye was measured immediately after eye opening. This measurement was then repeated on eye every 20 minutes over the first hour after eye opening and every hour for the subsequent 2 hours. The anterior segment was examined with a slit-lamp biomicroscope for safety purposes (with and without the instillation of fluorescein) after the last measurement.

Data Analysis
Statistical analyses were performed using statistical software (IBM SPSS, version 22 or higher; IBM SPSS, Inc., Armonk, NY, USA). The following mixed model analyses were conducted:

1. Analysis of corneal swelling (%) over the range of Dk/t of study lenses controlling for subjects’ age, and refractive error (autorefraction spherical equivalent) as covariates, sex as a fixed factor, and subject (intercept and/or slope) as a random factor(s). The intercept represents the level of CS following eye closure (with or without a lens) and the slope represents the rate of corneal deswelling per hour.

Lenses-wearing and contralateral control eyes (with no lens wear) were separately analyzed with mixed modeling of either swelling or deswelling data.

The mixed modeling procedure simultaneously estimates the fixed effect parameters for the observed data (i.e., group effects) and the variance of the random effects (i.e., between-subject effects). Several mixed models were iteratively constructed, beginning with linear models where only the intercept or the slope were modeled as random between-subject factors, moving to a more complex linear model where both the intercept and the slope were modeled as random between-subject factors, moving to a more complex linear model where both the intercept and the slope were modeled as random between-subject factors and, lastly, a curvilinear (quadratic) model with the intercept and slope as random between-subject factors. As part of the process of model selection, each model’s deviance (−2log likelihood) was computed. To compare between the fixed effect among progressively more complex models (nested), the log likelihood ratio test (LLRT) was used, which takes the difference in the deviance value for each model and tests whether the added complexity significantly improves the fit of the model by testing the magnitude of the LLRT to critical values of the χ² distribution (Accepting the null hypothesis, $H_0$, indicates that the added complexity does not improve the model fit; rejecting the null hypothesis indicates the converse). In addition, generally a parsimony criterion was used when model log likelihood ratios did not show a statistical difference; in these instances, the simplest model was accepted. The model fit was similarly evaluated for inclusion of 2- or 3-way interactions of the fixed effects. For the selected “best” models, the models were re-run to generate restricted −2log likelihood values with Hurvich and Tsai’s (AICC) criterion (which accounts for bias in log likelihood estimations with small sample sizes) to optimize the estimate of the variance of the random effects for the fitted model. The estimates from this model are those that are reported in the “Results” section.

To serve as a comparison with the more typical approach where between-subjects effects are not considered, a marginal (population average) linear/curvilinear model with

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### Table 2. Lens Parameters

<table>
<thead>
<tr>
<th>Lens Material</th>
<th>Manufacturer</th>
<th>Dk (cm²/s) × (mL O₂/mL mm Hg)</th>
<th>Central Dk/t (cm mL O₂)/(mL s mm Hg)</th>
<th>Lens Power, D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Night &amp; Day</td>
<td>Lotrafilcon A</td>
<td>CIBA Vision</td>
<td>140 × 10⁻¹¹</td>
<td>−10.00, −3.00, +6.00</td>
</tr>
<tr>
<td>Acuvue OASYS</td>
<td>Senofilcon A</td>
<td>Johnson &amp; Johnson Vision Care</td>
<td>105 × 10⁻¹¹</td>
<td>−10.00, −3.00, +6.00</td>
</tr>
<tr>
<td>PureVision</td>
<td>Balafilcon A</td>
<td>Bausch &amp; Lomb</td>
<td>91 × 10⁻¹¹</td>
<td>−10.00, −3.00, +6.00</td>
</tr>
<tr>
<td>Acuvue Advance</td>
<td>Galyfilcon A</td>
<td>Johnson &amp; Johnson Vision Care</td>
<td>60 × 10⁻¹¹</td>
<td>−10.00, −3.00, +6.00</td>
</tr>
</tbody>
</table>

* Nominal values for −3.00 D lens power.

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### Table 3. Lens Center Thickness (Mean ± SD) and Transmissibility (Dk/t) by Lens and Power

<table>
<thead>
<tr>
<th>Lens Material</th>
<th>Lens Center Thickness, μm</th>
<th>Lens Central Dk/t × 10⁻⁹ (cm mL O₂)/(mL s mm Hg)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lotrafilcon A</td>
<td>66 ± 4.7</td>
<td>199 ± 11.0</td>
<td>211</td>
</tr>
<tr>
<td>Senofilcon A</td>
<td>66 ± 2.5</td>
<td>198 ± 3.4</td>
<td>156</td>
</tr>
<tr>
<td>Balafilcon A</td>
<td>86 ± 3.8</td>
<td>194 ± 5.3</td>
<td>106</td>
</tr>
<tr>
<td>Galyfilcon A</td>
<td>62 ± 1.4</td>
<td>196 ± 2.9</td>
<td>96</td>
</tr>
</tbody>
</table>
only fixed effects was also run to determine if between-subject effects contributed statistically. Because this analysis in all cases, produced worse fits to the data compared to the mixed models these results (marginal models) are not reported here.

**RESULTS**

**Overnight CS (on Eye Opening) Versus Dk/t in Lens-Wearing and Control Eyes**

Central corneal swelling induced by overnight wear of the 12 SiHy lenses in the subjects as a function of central lens oxygen transmissibility is shown in the lens-wearing (left panel) and control eyes (right panel) in Figure 1. The best fit model for overnight corneal swelling versus Dk/t in both lens and control eyes was a linear model with a random intercept. To verify between-subject variability of the slope of the corneal swelling over Dk/t, we attempted to add a random slope in the model. However, the linear model with a random slope and the curvilinear model failed to converge (and so could not be computed) most likely due to a close-to-zero slope variance.

In the final linear model (with a random intercept), the mean intercept of the corneal swelling response was significantly greater than zero in both lens and control eyes. In this model there was a significant effect of lens Dk/t on corneal swelling in lens-wearing eyes (Table 4); this means that the slope of the swelling versus Dk/t function was statistically different from zero. However, we did not find any effect of lens Dk/t on corneal swelling in the control eyes with no lens wear (Table 4). Age, sex, and spherical equivalent of the refractive error in either lens or control eyes were also not statistically significant predictors of corneal swelling (Table 4). As the model converged only for a random intercept, 100% of the between-subject variance in the model was explained by the variance of the intercept (Table 5).

**Corneal Deswelling (the Function Relating CS to Time After Eye-Opening) in Lens-Wearing and Control Eyes**

The recovery from swelling (corneal deswelling) induced by overnight wear of the 12 SiHy lenses in the subjects during the 3-hour period after eye opening (and lens removal) is shown in Figure 2 (light lines). These can be compared to the linear fits averaged across individuals for the 12 lenses (bold lines) in the lens-wearing (left panel) and control eyes (right panel). There was a significant effect of time, Dk/t and age on corneal deswelling in the lens-wearing eyes (Table 6). However, in controls, only the effect of time was statistically significant (Table 6).

Analysis of the partitioned variances of the random effects in Table 7 showed that in the linear mixed model of the lens-wearing eye, 93% of the total between-subject variance (variance of intercept + variance of the slope) was due to total between-subject differences in the intercept and 7% of the variance was caused by the variance of the slope. Although the overall between-subject variance was 29% lower in the control eyes, interestingly, the same proportions of the total between-subject variances (93% for intercept, and 7% for slope) were found in the control eyes. The slope was inversely related to the intercept both in the lens or control eyes ($P = 0.01$ for both).

In the lens-wearing eyes, 9% of the between-subject variance of the intercept and 5% of the between-subject variance of the slope were because of the differences in Dk/t of the study lenses (Table 7). In the controls, the proportion of between-subject variances due to the differences in lens Dk/t consisted of 1% of the between-subject variance in the intercept and 5% of the between-subject variance in the slope, respectively (Table 7).

Based on the apparent shape of the individual distributions of corneal deswelling over time (Fig. 3), we also modeled the data using a curvilinear (quadratic) fit for both fixed and random effects (Fig. 4).
Mixed Modeling of Between-Subject Corneal Swelling

**Table 4.** Group Effects: Estimates of Fixed Effects* in the Linear Model With Random Between-Subjects Intercept of Overnight CS in Lens and Control Eyes as a Function of Lens Dk/t

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>df</th>
<th>t</th>
<th>Sig</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lens eye</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>7.156</td>
<td>1.339</td>
<td>25</td>
<td>5.345</td>
<td>0.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dk/t</td>
<td>−0.011</td>
<td>0.002</td>
<td>307</td>
<td>−5.755</td>
<td>0.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractive error</td>
<td>0.293</td>
<td>0.237</td>
<td>24</td>
<td>1.238</td>
<td>0.228</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.026</td>
<td>0.048</td>
<td>24</td>
<td>0.541</td>
<td>0.594</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, female</td>
<td>1.021</td>
<td>0.769</td>
<td>24</td>
<td>1.326</td>
<td>0.197</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, male</td>
<td>0†</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control eye</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>4.299</td>
<td>1.271</td>
<td>25</td>
<td>3.382</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dk/t</td>
<td>−0.002</td>
<td>0.002</td>
<td>307</td>
<td>−1.189</td>
<td>0.235</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refractive error</td>
<td>0.206</td>
<td>0.225</td>
<td>24</td>
<td>0.915</td>
<td>0.369</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>−0.005</td>
<td>0.046</td>
<td>24</td>
<td>−0.119</td>
<td>0.906</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, female</td>
<td>1.088</td>
<td>0.730</td>
<td>24</td>
<td>1.491</td>
<td>0.149</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, male</td>
<td>0†</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SE, standard error of the estimated parameter; df, degrees of freedom (rounded to integer); t, estimate of t-statistic; Sig, P value for t for the given df.

* Dependent variable: corneal swelling (%).
† This parameter is set to zero because it is redundant.

Similar to the linear mixed model, in the curvilinear mixed model of corneal deswelling, there were significant effects of time, oxygen transmissibility and age on corneal deswelling in the lens-wearing eyes (Table 8). Also, similar to the linear fit results, in the curvilinear model, time was the only significant predictor of control deswelling (Table 8).

The comparison between the linear and curvilinear models with random between-subject effects showed that the best fit in both lens-wearing and control eyes was the curvilinear mixed model with random intercept and random slope (Fig. 4). While the overall model (fixed and random effects) was best fit with a random intercept and random slope, examination of the partitioned between-subject variances (Table 9) indicates minimal contribution of the curvilinear slope (variance of 0.010 and 0.012 in lens and control eyes, respectively) to the between-subject variances in the curvilinear model.

**Discussion**

**Random Individual Contributions to Corneal Swelling**

We examined the effect of Dk/t on corneal swelling in lens-wearing and contralateral control eyes (no lens) using mixed modeling. Perhaps the most important finding here was that the best statistical description for overnight corneal swelling in both lens and control eyes was a linear random intercept model with no variation in the slope of the overnight corneal swelling across the range of Dk/t between subjects. To our knowledge, this is the first time that the structure of the overnight corneal swelling has been explored and reported, and the results highlight the importance of between-subject differences; some swell a little and others swell more, and the group mean swelling is not the best descriptor.

Our analysis revealed that the differences in CS among different subjects in either lens or control eyes remained constant (did not change) by a change in lens Dk/t. This means that, for the range of lens Dk/t of 31 to 211 units in this study, subjects exhibiting both lower and higher levels of corneal swelling consistently showed this across the whole Dk/t range. Those who swollen least to one lens, swollen least to the others and those who swollen most swollen most to all lenses. This again reinforces the simple notion that in evaluating the response to lenses of different Dk/t, the lens characteristics are important, but it is critical to consider the subject characteristics as well.

In the simultaneous analysis of fixed (overall) effects of CS we did not find a statistically significant effect of age, sex or refractive error on the magnitude of CS in either lens-wearing or control eyes. This is in line with lack of evidence for any of these predictors in the literature and suggests that the between-subject variability in corneal swelling could perhaps be explained by more complex underlying individual differences. Many other uncontrolled individual factors such as differences in the physical size of the globe, differences in palpebral conjunctival area, differences in palpebral conjunctival vessel density, palpebral conjunctival vessel permeability, corneal epithelial/endothelial morphologic variabilities could potentially impact the between-subject variability in corneal swelling. It may not be feasible to control for all possible individual differences that could possibly impact the CS in a single study. However, based on the literature, we suggest adding individual measures of corneal oxygen demand (corneal...
metabolic activity) and a measure of individual endothelial morphologic variability (endothelial function) in a future mixed model analysis to investigate other biologically plausible predictors of between-subject differences in corneal swelling.

The analysis of the between-subject (random effect) variances in our study showed that the between-subject variability in CS was not dependent on Dk/t despite corneal swelling itself (obviously) being dependent on Dk/t. Put simply, the difference between subjects existed independently of the lens Dk/t inducing the swelling. In addition, individual CS responses for the entire range of Dk/t could be predicted from a response of an individual to a single Dk/t using the overall slope of CS over Dk/t. This is because of lack of difference among individual slopes of CS over the range of Dk/t in the best fit model (random intercept model of corneal swelling; Fig. 1, Table 5).

**Random Individual Contributions to Corneal Deswelling**

We examined the recovery of corneal swelling in lens-wearing and contralateral control eyes (no lens) over the 3-hour period from a response of an individual to a single Dk/t using the overall slope of CS over Dk/t. This is because of lack of difference among individual slopes of CS over the range of Dk/t in the best fit model (random intercept model of corneal swelling; Fig. 1, Table 5).

### Table 6. Group Effects: Estimates of the Fixed Effects* in the Linear Model With Random Intercept and Random Slope for Corneal Deswelling Following Overnight Lens Wear in Lens-Wearing and Control Eyes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>df</th>
<th>t</th>
<th>Sig.</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lens eye</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>5.373</td>
<td>0.612</td>
<td>40</td>
<td>8.774</td>
<td>0.000</td>
<td>4.135</td>
<td>6.610</td>
</tr>
<tr>
<td>Time</td>
<td>−2.105</td>
<td>0.125</td>
<td>27</td>
<td>−16.880</td>
<td>0.000</td>
<td>−2.561</td>
<td>−1.849</td>
</tr>
<tr>
<td>Dk/t</td>
<td>−0.011</td>
<td>0.003</td>
<td>10</td>
<td>−3.558</td>
<td>0.005</td>
<td>−0.018</td>
<td>−0.004</td>
</tr>
<tr>
<td>Time × Dk/t</td>
<td>0.003</td>
<td>0.001</td>
<td>10</td>
<td>4.176</td>
<td>0.002</td>
<td>0.001</td>
<td>0.005</td>
</tr>
<tr>
<td>Age</td>
<td>0.037</td>
<td>0.013</td>
<td>24</td>
<td>2.884</td>
<td>0.008</td>
<td>0.011</td>
<td>0.064</td>
</tr>
<tr>
<td>Refractive error</td>
<td>−0.002</td>
<td>0.063</td>
<td>24</td>
<td>−0.035</td>
<td>0.973</td>
<td>−0.132</td>
<td>0.128</td>
</tr>
<tr>
<td>Sex, female</td>
<td>−0.278</td>
<td>0.204</td>
<td>24</td>
<td>−1.361</td>
<td>0.186</td>
<td>−0.699</td>
<td>0.144</td>
</tr>
<tr>
<td>Sex, male</td>
<td>0†</td>
<td>0</td>
<td></td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td><strong>Control eye</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>1.611</td>
<td>0.575</td>
<td>43</td>
<td>2.805</td>
<td>0.008</td>
<td>0.452</td>
<td>2.770</td>
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<tr>
<td>Time</td>
<td>−1.053</td>
<td>0.103</td>
<td>26</td>
<td>−10.226</td>
<td>0.000</td>
<td>−1.265</td>
<td>−0.842</td>
</tr>
<tr>
<td>Dk/t</td>
<td>−0.002</td>
<td>0.002</td>
<td>9</td>
<td>−1.064</td>
<td>0.314</td>
<td>−0.006</td>
<td>0.002</td>
</tr>
<tr>
<td>Time × Dk/t</td>
<td>−0.000</td>
<td>0.001</td>
<td>9</td>
<td>−0.529</td>
<td>0.609</td>
<td>−0.002</td>
<td>0.001</td>
</tr>
<tr>
<td>Age</td>
<td>0.022</td>
<td>0.017</td>
<td>24</td>
<td>1.296</td>
<td>0.207</td>
<td>−0.013</td>
<td>0.058</td>
</tr>
<tr>
<td>Refractive error</td>
<td>−0.042</td>
<td>0.084</td>
<td>24</td>
<td>−0.494</td>
<td>0.626</td>
<td>−0.216</td>
<td>0.132</td>
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<td>Sex, female</td>
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<td>0.729</td>
<td>0.473</td>
<td>−0.366</td>
<td>0.765</td>
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<tr>
<td>Sex, male</td>
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<td>0</td>
<td></td>
<td>−</td>
<td>−</td>
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<td>−</td>
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</tbody>
</table>

* Dependent Variable: corneal swelling (%).
† This parameter is set to zero because it is redundant.
after eye opening (and lens removal) using mixed modeling. In general, our results showed that there was a difference in swelling (model intercept) and deswelling (model slope). In the linear deswelling model in both lens and control eyes (Fig. 2), our analysis revealed that the between-subject variability in corneal deswelling function was mostly due to between-subject differences in their intercept, with less contribution from the function’s slope. Also, the between-subject differences in corneal deswelling function in lens-wearing eyes was minimally affected by wearing 12 different lenses (Dk/t values) in the 12 study nights (Table 7).

The between-subject variances of the squared term of the slope (Time^2) in the curvilinear model were close to zero, contributing to only 0.25% and 0.37% of the total between-subject variance in lens-wearing and control eyes, respectively (Table 9). This indicates that this random effect (between-subject variability in the rate of deswelling), in either lens wearing or control eyes, was largely linear. Therefore, the between-subject variability of corneal deswelling can similarly be described by the between-subject variances of the linear function in either linear or curvilinear models of corneal deswelling. This confirms sufficiency of the linear term for explaining the random effects in corneal deswelling, and that it could be considered as a parsimonious substitute for the more complex curvilinear model of corneal deswelling. The main advantage of using the more complex curvilinear model would be its improved intercept and slope estimates.

Subject sex and refractive error were not predictors of individual corneal deswelling functions in lens-wearing or control eyes in our analysis. In lens-wearing eyes only, however, there was a decrease in deswelling rate of ~0.04% per hour by each additional year of age (Table 8, P = 0.008). Our finding of slower recovery from corneal swelling in older age is in line with findings from previous studies, with statistically significantly slower recovery of corneal swelling in older compared to younger groups after 2 hours of closed eye CL wear. It is also worth noting that these previous studies did not control for any no-lens wear. The slower corneal deswelling rate in older individuals might be attributed (among other things) to lower endothelial pump function in older age. An association between endothelial morphological changes and endothelial pump function (recovery from swelling) was found in both normal and diseased corneal endothelium in the past.

Overall Discussion

Our study was not designed to stratify age and the oldest subject in our study was only 50 years old. Despite this rather truncated age sampling, our data buttress previous reports that age does affect corneal deswelling. We did not find any other results from the fixed effects analyses of either corneal swelling and/or deswelling models that could be deemed unexpected/surprising. This provides some evidences for external/internal validity of the mixed modeling analysis approach in our study.

To our knowledge, this is the first report on simultaneous modeling of fixed (average) and random (subject) effects in corneal swelling or deswelling. Our analyses of the random subject effects of CS over the range of Dk/t of study lenses provides support for the random intercept model to best explain the between subject variability in CS in either lens-
wearing or control eyes. The corneal deswelling functions, in either lens or control eyes, could be best explained by random intercept and slope models. The between-subject differences in both corneal swelling over Dk/t (Fig. 1) and corneal deswelling over time (Figs. 2, 4) functions were not dependent on lens Dk/t. This detailed insight could not be revealed through average analysis/analysis of fixed effects (ANOVA or regression analysis). Furthermore, the average analysis is prone to measurement errors from Simpson’s paradox and that by averaging among the study clusters (in this context, high-swimmers and low-swimmers and their rate of deswelling), other relationships within the data may be masked or reversed. In addition, the mixed model analysis can concurrently investigate the impact of other factors or covariates that might

FIGURE 4. Curvilinear (quadratic) regressions for individual corneal deswelling versus time after eye opening (light lines) and averaged across subjects (bold lines) for each lens Dk/t in lens-wearing and control eyes (left and right, respectively; black bold line: grand mean curvilinear trajectory). In comparison to Figure 2 with linear fitted functions, this graph shows that curvilinear functions also fit the data well, with similar random effects to Figure 2. On the left, a general gradation of warm to cool colors (low to higher Dk/t respectively) is apparent, whereas that is not the case in the control (nonlens wearing eye).


<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>df</th>
<th>t</th>
<th>Sig</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower Bound</td>
</tr>
<tr>
<td>Lens eye</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td>6.874</td>
<td>0.627</td>
<td>43</td>
<td>10.963</td>
<td>0.000</td>
<td>5.609</td>
</tr>
<tr>
<td>Time</td>
<td>−5.501</td>
<td>0.248</td>
<td>102</td>
<td>−22.217</td>
<td>0.000</td>
<td>−5.992</td>
</tr>
<tr>
<td>Time²</td>
<td>1.042</td>
<td>0.060</td>
<td>207</td>
<td>17.538</td>
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<td>0.923</td>
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<td>Dk/t</td>
<td>−0.015</td>
<td>0.003</td>
<td>11</td>
<td>−4.002</td>
<td>0.000</td>
<td>−0.020</td>
</tr>
<tr>
<td>Time × Dk/t</td>
<td>0.007</td>
<td>0.002</td>
<td>167</td>
<td>4.081</td>
<td>0.000</td>
<td>0.003</td>
</tr>
<tr>
<td>Time² × Dk/t</td>
<td>−0.001</td>
<td>0.000</td>
<td>306</td>
<td>−2.523</td>
<td>0.012</td>
<td>−0.002</td>
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<tr>
<td>Age</td>
<td>0.037</td>
<td>0.013</td>
<td>24</td>
<td>2.873</td>
<td>0.008</td>
<td>0.010</td>
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<tr>
<td>Refractive error</td>
<td>−0.006</td>
<td>0.063</td>
<td>24</td>
<td>−0.088</td>
<td>0.930</td>
<td>−0.135</td>
</tr>
<tr>
<td>Sex, female</td>
<td>−0.284</td>
<td>0.203</td>
<td>24</td>
<td>−1.396</td>
<td>0.176</td>
<td>−0.704</td>
</tr>
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<td>Sex, male</td>
<td>0†</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Control eye‡</td>
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<tr>
<td>Intercept</td>
<td>3.289</td>
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<td>51</td>
<td>5.674</td>
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<td>Time</td>
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<td>29</td>
<td>−21.818</td>
<td>0.000</td>
<td>−3.993</td>
</tr>
<tr>
<td>Time²</td>
<td>0.761</td>
<td>0.032</td>
<td>56</td>
<td>23.561</td>
<td>0.000</td>
<td>0.696</td>
</tr>
<tr>
<td>Dk/t</td>
<td>−0.002</td>
<td>0.002</td>
<td>10</td>
<td>−1.329</td>
<td>0.214</td>
<td>−0.006</td>
</tr>
<tr>
<td>Age</td>
<td>0.021</td>
<td>0.016</td>
<td>27</td>
<td>1.265</td>
<td>0.216</td>
<td>0.013</td>
</tr>
<tr>
<td>Refractive error</td>
<td>−0.059</td>
<td>0.081</td>
<td>27</td>
<td>−0.483</td>
<td>0.635</td>
<td>−0.204</td>
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<tr>
<td>Sex, female</td>
<td>0.172</td>
<td>0.262</td>
<td>27</td>
<td>0.655</td>
<td>0.518</td>
<td>−0.366</td>
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<tr>
<td>Sex, male</td>
<td>0†</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Dependent Variable: Corneal swelling (%).
† This parameter is set to zero because it is redundant.
‡ Insignificant interactions between Dk/t × Time ($P = 0.969$), and between Dk/t × Time² ($P = 0.864$) were removed to improve the fit of the model.
Control eye

subject variation: This demonstrates statistically that there is a
variables (age, sex, or refractive error). We showed that there
from any of the subject-related controlled independent
CS responses could not be predicted from the overall results or
effects simultaneously. Our analysis confirmed that individual
enabled us to analyze both the between-subject and the fixed
structure of CS to more adequately understand CL induced CS
specifically add an analysis of the between-subject random

CONCLUSIONS

tools. Therefore, it is reasonable, where possible, to use the
lenses with the highest oxygen transmissibility to minimize the
risk of corneal oxygen deficiency in closed-eye lens wear, and
examine each individual’s swelling response to the lens.

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Care (F), Ocular Dynamics (F), Oculus (F), Saffilens (F), TearLab (F),
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Inc. (C); T.L. Simpson, None

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Mixed Modeling of Between-Subject Corneal Swelling

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Table 9. Estimates of Variances of Random Effects in the Curvilinear Random Intercept and Random Slope Model for Overnight Corneal Deswelling in Lens-Wearing and Control Eyes

<table>
<thead>
<tr>
<th>Source of Variance</th>
<th>Intercept Variance</th>
<th>Slope Variance</th>
<th>Correlation†</th>
<th>Slope² Variance</th>
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</thead>
<tbody>
<tr>
<td>Lens eye</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Between subject (except Dk/t)</td>
<td>3.368</td>
<td>0.538</td>
<td>−0.94</td>
<td>0.010</td>
</tr>
<tr>
<td>Between subject (Dk/t)</td>
<td>0.289</td>
<td>0.011</td>
<td>−0.76</td>
<td>†</td>
</tr>
<tr>
<td>Control eye</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between subject (except Dk/t)</td>
<td>2.845</td>
<td>0.567</td>
<td>−0.97</td>
<td>0.012</td>
</tr>
<tr>
<td>Between subject (Dk/t)</td>
<td>0.031</td>
<td>0.005</td>
<td>0.07</td>
<td>†</td>
</tr>
</tbody>
</table>

* Correlation between random intercept and random slope.
† Could not be computed.

explain why some individuals behave differently (such as the
effect of age on corneal deswelling). This analysis enabling the
combination of random and fixed effects provides novel
insights into, and therefore examination of testable theories of
how, subject variability contributes to the outcome in ways
not possible using more “traditional” methods.

In addition to statistically demonstrating the presence of
between-subject variability in overnight CS, the analysis also
points to smaller differences between individual corneal
deswelling rates after eye opening, irrespective of lens Dk/t.
The negative correlation between the random intercept and
random slope of corneal deswelling function shows that there
is a faster deswelling rate with greater initial swelling.

Following the removal of hypoxic stress, individual
deswelling responses in this study were mainly affected by
their differences in the intercept of the corneal deswelling
function. This was demonstrated by the main proportion ~90% of
the total between-subject variance in either lens or control
eyes being due to between-subject differences in the intercept
with much less (~10%) of the between-subject variance being
due to the variability of the slope (or in the individual corneal
deswelling rate). As can be seen in Figures 2 through 4, the
small increase in the individual deswelling rate (from the
inverse relation between random intercept and random slope
in Table 7) in higher swellers was not enough to produce the
convergence of their individual deswelling functions, so they
did not all cross the time axis for zero swelling at the same
point as did the lower swellers. Therefore, although higher
swelling individuals deswelled slightly faster, it would generally
still take them longer than lower swellers to reach the baseline
level. The incomplete recovery of higher swellers at 3 hours
after lens removal is evident in the same images (Figs. 2–4).

CONCLUSIONS

Our goal from mixed model analysis of corneal swelling, was to
specifically add an analysis of the between-subject random
structure of CS to more adequately understand CI, induced CS
in closed eye conditions and corneal deswelling over time
when eyes were subsequently opened. Mixed modeling enabled
us to analyze both the between-subject and the fixed
effects simultaneously. Our analysis confirmed that individual
CS responses could not be predicted from the overall results or
from any of the subject-related controlled independent
variables (age, sex, or refractive error). We showed that there
are large statistical components in the model due to between-
subject variation. This demonstrates statistically that there is a
range of swelling (“low swellers” to “high swellers”) in a
group of participants. For a new patient in the chair during a
routine clinical visit, it would be impossible to determine
whether they are a higher or low sweller using routine clinical
methods.


