Epithelial Thickness Changes from the Induction of Myopia with CRTH RGP Contact Lenses

Sameena Haque, Desmond Fonn, Trefford Simpson, and Lyndon Jones

PURPOSE. To investigate changes in epithelial thickness after overnight wear of CRTH rigid gas-permeable (RGP) lenses (Paragon Vision Sciences, Mesa, AZ) for the correction of hyperopia.

METHODS. Twenty subjects wore a +3.50 D hyperopia-correcting CRTH lens on one eye for a single night in an attempt to induce myopia (first study). The untreated eye served as the control. Corneal and epithelial thickness was measured at nine points across the horizontal meridian by OCT. Measurements were obtained the night before lens wear, immediately after lens removal the next morning, and 1, 3, 6, and 12 hours after removal. Measurements were obtained 28 hours later, to observe recovery. Then, the attempted hyperopic corrections of +1.50 and +3.50 D were evaluated, using CRTH lenses in both eyes of 20 subjects for a single night (second study).

RESULTS. All values were compared to baseline unless otherwise stated. In the first study, the treated eye’s central and midperipheral epithelial thickness increased by 21.5% ± 8.6% and 13.3% ± 7.6%, respectively, after lens removal (P < 0.001). The control eye’s central epithelial thickness (CET) increased by 7.1% ± 6.0% (P < 0.05). In the second study, CET increased by 17.6% ± 8.5% (P < 0.001) in the +3.50 D–treated eye and by 13.3% ± 4.8% (P < 0.001) in the +1.50 D–treated eye. Midperipheral epithelial thickening was 5.9% ± 4.7% (P < 0.05) in the +3.50 D–treated eye and 6.0% ± 6.5% (P < 0.05) in the +1.50 D–treated eye.

CONCLUSIONS. CRTH lenses, designed to correct hyperopia, when worn overnight, caused an increase in CET. The amount of epithelial change seemed to differ with modified lens design. (Invest Ophthalmol Vis Sci. 2008;49:3345–3350) DOI:10.1167/iovs.07-1996

Corneal refractive therapy (CRT) is a modern term for orthokernatology, the programmed application of rigid gas-permeable (RGP) contact lenses to reduce refractive error. These lenses are worn overnight to reshape the cornea, providing a temporary but reasonable improvement in vision that recovers gradually throughout the day. To date, orthokeratolgy has focused on the treatment of myopia, using lenses to cause central corneal flattening and midperipheral steepening. Consequently, it is assumed that a lens of the opposite design may allow the cornea to steepen and thicken centrally and to flatten and become thinner in the midperiphery. The final result would be a lens that corrects hyperopia rather than myopia.

Swarbrick et al.1 recently used steeply fitted rigid lenses with apical clearance to induce corneal steepening and hence a myopic shift. In this study, two sets of conoid lenses (PMMA and Boston XO; Bausch & Lomb, Rochester, NY) were worn in the open eye for 4 hours. Both lenses steepened the cornea, but the resultant increase in myopia was slight (0.32 D) and failed to reach statistical significance. However, the authors did not report any epithelial changes.

Choo et al. (JOVS 2004;45:ARVO E-Abstract 1552) reported a study on hyperopic CRT (CRTH; Paragon Vision Sciences, Mesa, AZ) in which they examined histologic changes in the feline corneal epithelium. Light microscopy images (in which epithelial thickness was calculated using image measurement software) showed the epithelium, but contrary to what was seen with a subsequent thinning of the midperipheral epithelium, opposite the changes seen after myopic CRT. In the five cats examined, the central epithelium had thickened on average by 146% (54 μm) after the lenses had been worn continuously for 2 weeks. The report displayed images that indicated a large degree of central stromal thickening after 14 days of CRTH lens wear.

Recently, Lu et al.2 measured in vivo corneal and epithelial changes in human subjects, and found the pattern of central and midperipheral thickness change to be opposite between CRTH and CRT treatments. After 60 minutes of closed-eye hyperopic correction, the epithelium thickened ~1.7% in both the central and midperipheral regions.

The purpose of this study was to measure and compare the change in epithelial thickness after CRTH lens (Paragon Vision Sciences) wear, by inducing myopic defocus or correcting different amounts of hyperopia. Optical coherence tomography (OCT) was used to measure thickness across the horizontal corneal meridian. OCT is an in vivo technique for high-resolution, cross-sectional imaging, in which optical interferometry is used to determine the distance between reflective structures within the eye.3–5

METHODS

Subjects

Informed consent was obtained from each participant (adhering to the tenets of the Declaration of Helsinki), and ethics clearance was obtained from the Office of Research Ethics at the University of Waterloo, before commencement of the study. Each subject presented without history of ocular disease or surgery. There were no enrollment restrictions on the type of refractive error, but participants with emmetropia or hypertropia were preferred. Participants with low myopia (<1.50 DS) were permitted into the study, only with the understanding that they might become more myopic (for which spectacles were available for temporary use until the cornea recovered). Spherical error was limited to +3.00 D, with no more than −1.50 D cylinder. Current RGP lens wearers were excluded, and soft lens wearers had to discontinue lens wear 2 weeks before the start of the study. Twenty healthy subjects were enrolled in each study (the first study: 15 females and 5 males; mean age 20.1 ± 7.5 years; range: 22–48; and the second study: 10 females and 10 males; mean age, 29.0 ± 8.5 years; range, 20-44 years). Tables 1 and 2 summarize the corneal parameters of the cohorts used in each study.
TABLE 1. Corneal Parameters before the Commencement of Study 1

<table>
<thead>
<tr>
<th>CRTH (+3.50 D) Eye</th>
<th>Control Eye</th>
</tr>
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<tbody>
<tr>
<td>Refractive error, sphere (D)</td>
<td>−1.86 ± 2.64</td>
</tr>
<tr>
<td>Refractive error, cylinder (D)</td>
<td>−0.56 ± 0.42</td>
</tr>
<tr>
<td>Keratometry, flat K (D)</td>
<td>43.14 ± 1.78</td>
</tr>
<tr>
<td>Keratometry, cylinder (D)</td>
<td>−0.71 ± 0.42</td>
</tr>
<tr>
<td>Central corneal thickness (µm)</td>
<td>508.8 ± 27.0</td>
</tr>
<tr>
<td>Central epithelial thickness (µm)</td>
<td>52.5 ± 2.6</td>
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</tbody>
</table>

Data are the mean baseline corneal parameters ± SD.

Instrumentation and Lenses

A retinal OCT2 (model 2010; Carl Zeiss Meditec, Dublin, CA) was used to measure corneal thickness, across the horizontal meridian. The OCT2 uses a superluminescent diode (SLD) near-infrared light source operating at a wavelength of 820 nm. The bandwidth of the light source governs the axial resolution available for imaging, in this case being 10 to 20 µm, which is inadequate to image the cornea at the cellular level, but can distinguish the epithelial layer from the stroma. A boundary is detected when there is a change in refractive index through the cornea and is displayed with a peak in a light backscatter profile produced (discussed in detail previously). It is the difference between these boundaries that enables the calculation of corneal and epithelial thickness. Thicknesses were not available at a glance from this OCT. Custom software designed by the Center for Contact Lens Research (CCLR) enabled multiple pixel analysis per scan to yield a value for average thickness across that scan, in an automated fashion.

Images were taken at 1° intervals across a 10 mm chord, with a fixation device mounted on the instrument (described previously). The light-emitting diodes (LEDs) were located nasally and temporally to the central fixation light at approximately 0.8, 1.6, 2.7, and 3.6 mm from the center. Each cross section of cornea scanned was 1.13 mm in length and enabled the compilation of a thickness profile from limbus to limbus across the horizontal meridian.

The CRTH lenses (Paragon Vision Sciences, Mesa, AZ) used in both studies were manufactured from fluorosilicone acrylate with an oxygen permeability (Dk) of 100 × 10−11 and transmissibility (Dk/t) of 67 × 10−9. The lenses were fit with software provided by the manufacturer. The lenses selected by the program were assessed on-eye, to ensure that there was appropriate apical clearance (4 mm wide), midperipheral touch, adequate edge lift, and proper centration (Fig. 1). The parameters for the lenses used in studies 1 and 2 are listed in Tables 3 and 4, respectively. For each subject, the eye to be treated with a specific lens was assigned at random. In the first study, one eye wore a lens designed to induce +3.50 D of myopic defocus (or treat hyperopia). The contralateral eye did not wear a lens and acted as the control.

In the second study, each eye was randomly assigned to wear a lens to induce either +3.50 or +1.50 D of myopia (or treat hyperopia). The back optic zone radius (BOZD) was calculated by subtracting 0.7 mm from the flat K reading for the +3.50 D lens fitting, and 0.3 mm for the +1.50 D fitting.

TABLE 2. Corneal Parameters before the Commencement of Study 2

<table>
<thead>
<tr>
<th>+3.50 D Eye</th>
<th>+1.50 D Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractive error, sphere (D)</td>
<td>−1.16 ± 1.27</td>
</tr>
<tr>
<td>Refractive error, cylinder (D)</td>
<td>−0.55 ± 0.38</td>
</tr>
<tr>
<td>Keratometry, flat K (D)</td>
<td>43.49 ± 1.15</td>
</tr>
<tr>
<td>Keratometry, cylinder (D)</td>
<td>−0.52 ± 0.33</td>
</tr>
<tr>
<td>Central corneal thickness (µm)</td>
<td>513 ± 35.1</td>
</tr>
<tr>
<td>Central epithelial thickness (µm)</td>
<td>52.1 ± 2.2</td>
</tr>
</tbody>
</table>

Data are the mean baseline corneal parameters ± SD.

Procedures

In the evening before the sleepover, baseline corneal thickness measurements across the horizontal meridian were recorded. The CRTH lenses were inserted, and the fit was assessed for adequate movement, centration, and fluorescein pattern before sleep. Participants slept at the CCLR, retiring at 10 PM and waking at 7 AM the next morning. On waking, the subjects kept their eyes closed until the lenses were removed. In study 1, the thickness of each eye was measured immediately after lens removal and repeated 1, 3, 6, and 12 hours thereafter. An additional set of readings was obtained the next day (28 hours after initial lens removal) to monitor recovery. In study 2, an additional measurement was added at 20 minutes and then repeated at 1, 2, and 3 hours after lens removal.

Data Analysis

Raw data files captured by the OCT were processed with custom software designed at the CCLR. Values for epithelial thickness were calculated by the subtraction of stromal thickness from total corneal thickness. Midperipheral values were taken as the average of the two points either side of the center (location, 2.2 mm). Analysis of the thickness measurements was performed with commercial software (Statistica 6.0; Statsoft Inc, Tulsa, OK). Repeated measures analysis of variance (re-ANOVA), paired Student’s t-tests and Tukey HSD (honestly significantly different) post hoc testing was used to analyze changes in epithelial thickness from baseline levels and between corneal locations, comparing the center with the midperipheral region. The chosen level for significance was 0.05. The changes in thickness were compared to baseline values (unless otherwise stated) and expressed as percentage differences (mean ± SD): (thicknessbaseline − thicknesstime)/(thicknessbaseline) × 100.

TABLE 3. CRT H Lens Parameters Used in Study 1

<table>
<thead>
<tr>
<th>Parameters</th>
<th>+3.50 Lens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total diameter (mm)</td>
<td>10.5</td>
</tr>
<tr>
<td>BOZR (±SD mm)</td>
<td>7.19 ± 0.32</td>
</tr>
<tr>
<td>BOZD (mm)</td>
<td>5.2 ± 3.5</td>
</tr>
<tr>
<td>Return zone depth (±SD µm)</td>
<td>656 ± 38.0</td>
</tr>
<tr>
<td>Landing zone angle (±SD degrees)</td>
<td>34.0 ± 1.0</td>
</tr>
<tr>
<td>Power (D)</td>
<td>+0.50</td>
</tr>
<tr>
<td>Central thickness (mm)</td>
<td>0.17</td>
</tr>
<tr>
<td>Dk/t (barrers)</td>
<td>67</td>
</tr>
</tbody>
</table>
RESULTS

All subjects completed their respective studies. From the first study, Figure 2 shows the average changes in epithelial thickness in both the experimental and control eyes after a single night of CRTH lens wear. At lens removal, the epithelium of the lens-wearing eye had thickened by 21.5% ± 8.6% centrally and 13.3% ± 7.6% midperipherally (both P < 0.001). At the same time, in the control eye the epithelium thickened by 7.1% ± 6.0% centrally and 6.9% ± 6.4% midperipherally (both P < 0.05). Central and midperipheral changes were significantly different between eyes (P < 0.05). The epithelium recovered gradually throughout the day, the central remaining insignificantly thicker by 2.6% ± 5.6% at hour 12 (P > 0.05). After 28 hours without lens wear, epithelial thickness in the CRTH eye recovered by 98.5% centrally and 97.2% midperipherally (P > 0.05).

Figure 3 shows the average changes in corneal thickness in both the experimental and control eyes after a single night of CRTH lens wear. Corneal swelling in the experimental eye was greatest immediately after lens removal, measuring 8.8% ± 2.2% centrally and 8.1% ± 2.5% midperipherally (P < 0.001). Midperipheral values are represented by the mean of two points on either side of the center (four points in total). At lens removal the control eye swelled by 5.1% ± 1.6% centrally and 2.6% ± 1.3% midperipherally (both P < 0.001). The change in central corneal swelling at lens removal between eyes was statistically significant (P < 0.001). Both eyes demonstrated rapid corneal deswelling and recovered to baseline levels within 3 hours (P > 0.05).

In the second study, at lens removal, the +3.50 D–treated eye showed average central epithelial thickening of 17.6% ± 8.5% (P < 0.001) and the +1.50 D–treated eye showed 13.3% ± 4.8% (P < 0.001, Fig. 4). This central effect was significantly different between eyes (P < 0.05). The midperipheral epithelium thickened by 5.9% ± 4.7% in the +3.50 D–treated eye (P < 0.05) and 6.0% ± 6.3% in the +1.50 D–treated eye (P < 0.05). These midperipheral changes were not significantly different between eyes (P < 0.05). Central epithelial thickness in both eyes had not recovered to baseline after 3 hours (P < 0.05).

Regarding total corneal thickness, the +3.50 D–treated eye showed average central and paracentral corneal swelling of 6.9% ± 2.9% and 6.3% ± 3.3%, respectively, at lens removal (P < 0.05, Fig. 5). The +1.50 D–treated eye showed central and paracentral corneal swelling of 5.9% ± 3.1% and 6.2% ± 2.5%, respectively, at lens removal (P < 0.05). Corneal swelling in both eyes was not significantly different from baseline at 3 hours (P > 0.05).

DISCUSSION

This study showed significant increases in epithelial and corneal thickness after a single night of CRTH lens wear. The meridional pattern of epithelial change was opposite to that seen after CRT treatment for myopia, where the central epithelium thins and midperiphery thickens.20–22 The epithelium has been pronounced to be remarkably malleable, transforming under an orthokeratology lens or a combination of all these factors (Choo JD, et al. IOVS 2005;46:ARVO E-Abstract 2061).

The underlying causes that led to the substantial increases of epithelial thickness are still unclear, but there are several possibilities. The negative pressure caused by the postlens tear film, and the positive pressure of the contact zone of the lens surrounding the central clearance area (mechanical forces) are favored.20–22 The epithelium has been pronounced to be remarkably malleable, transforming under an orthokeratology (OK) lens with eye closure in as little as 10 minutes.22,24 Current theories behind the mechanism of epithelial thickness change include cell redistribution, cell compression with fluid transfer, inhibition of cell desquamation, increased cell mitosis, or a combination of all these factors (Choo JD, et al. IOVS 2004;45:ARVO E-Abstract 1552).20,25 Epithelial cell redistribution would be encouraged by the tear film forces beneath the OK lens, molding the epithelium to take the shape of the lens profile. Positive pressures would represent a

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<tr>
<td>BOZR (±SD mm)</td>
<td>7.19 ± 0.18</td>
<td>7.49 ± 0.23</td>
</tr>
<tr>
<td>BOZD (mm)</td>
<td>2.5–3.5</td>
<td>2.5–3.5</td>
</tr>
<tr>
<td>Return zone depth (± SD μm)</td>
<td>668 ± 14.28</td>
<td>680 ± 10.26</td>
</tr>
<tr>
<td>Landing zone angle (±SD degrees)</td>
<td>33.45 ± 0.89</td>
<td>33.45 ± 1.05</td>
</tr>
<tr>
<td>Power (D)</td>
<td>+0.50</td>
<td>+0.50</td>
</tr>
<tr>
<td>Center thickness (mm)</td>
<td>0.17</td>
<td>0.17</td>
</tr>
<tr>
<td>Dk/t (barrers)</td>
<td>67</td>
<td>67</td>
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</table>

FIGURE 2. Epithelial thickness changes across the horizontal corneal meridian after a single night of CRTH lens wear for myopic induction or hyperopic correction of +3.50 D in one eye, with the contralateral eye serving as a control (no lens worn). Vertical bars, 95% confidence level.

FIGURE 3. Corneal thickness changes across the horizontal meridian after a single night of CRTH lens wear for myopic induction or hyperopic correction of +3.50 D in one eye, with the contralateral eye serving as a control (no lens worn). Vertical bars, 95% confidence level.
"push" force, leading to a thinning in the epithelium, with negative pressures creating a "pull" force, leading to a thickening of the epithelium.20,22,26

Central and paracentral corneal swelling were partly due to hypoxia from the CRTH lens, which had a Dk/t of $67 \times 10^{-10}$. The swelling results in these studies by Wang et al.4 and Haque et al.5 were less than that found in this study, primarily because of the lens design differences. The CRT or OK lenses are designed to flatten the center of the cornea to reduce the myopic error unlike the design used in this study where the center of lens vaults the cornea (see Fig. 1), thus maintaining a fairly large volume of tear fluid between the lens and the central cornea.

The entrapment of tear fluid under a lens during overnight wear is a plausible cause of epithelial thickness change, particularly as rigid lenses (including CRT lenses) have been known to adhere to the cornea during eye closure.5 The epithelium is thought to imbibe the fluid behind the vaulted area of the lens (due to an imbalance in the osmotic pressure gradient), in effect causing an increase in epithelial thickness.

Epithelial cell redistribution, including cell compression after OK, has been shown in histologic images. Although these experiments were not performed in humans, these studies reported a reduction in the number of cell layers and a flattening of cells centrally, after OK for myopia. In the same studies, midperipheral regions of epithelial thickening consisted of an increase in cell layers, and an elongation of epithelial basal cells. The opposite was found in eyes that underwent OK for hyperopia (Choo JD, et al. IOVS 2004;45:ARVO E-Abstract 1552).27

One aspect of epithelial redistribution involves the actual migration of cells from an area of flattening (thinning) to an area of thickening. The possibility of this occurring has been questioned, due to the presence of desmosomes that cause epithelial cells to adhere to each other. These intercellular links would have to be broken for individual cells to migrate. It has been suggested that the pressure from an OK contact lens may be enough of a stimulus to enable this to occur.20 Considering these mechanisms explaining epithelial change after OK, increased cell mitosis seems the least likely, as many studies have shown that contact lenses in fact suppress epithelial metabolism.25,28–36

The amount of central epithelial thickening found in this study is far greater than that measured by Lu et al.,2 which
could be attributed to the length of time the lenses were worn in our study. The most notable difference between the epithelial results in this study compared with Choo et al. (IOVS 2004;45:ARVO E-Abstract 1552) and Lu et al., the lack of midperipheral epithelial thinning measured. Although there was a large increase in central epithelial thickness, the midperipheral epithelium did not exhibit the thinning that was anticipated from the contact or touch area of the lens surrounding the central clearance zone. Unforeseen findings such as this have been found in other studies investigating changes after myopic correction with OK, where central epithelial thinning was accompanied by an absence of midperipheral epithelial thickening.

With regard to reversibility of the CRTH procedure, as was the case in our myopic study, the epithelium recovered. In summary, overnight CRTH lens wear induced epithelial thickness changes. The anticipated difference in epithelial thickness changes by induction of myopic defocus corresponded with the lens design. The results suggest that different amounts of hyperopia may be corrected by various designs of CRTH the lens design. The results suggest that different amounts of hyperopia may be corrected by various designs of CRTH lenses, reaffirming the malleability of the epithelium.

Acknowledgments
The authors thank Paragon Vision Sciences and the Canada Foundation for Innovation (CFI) for assistance.

References


