Prominent Decrease of Superior Midperipheral Endothelial Cell Density After Iris-fixated Phakic Intraocular Lens Implantation

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ABSTRACT

PURPOSE: To evaluate changes in endothelial cell density (ECD) in the corneal region after implantation of an iris-fixated phakic intraocular lens (PIOL).

METHODS: Forty-five eyes of 25 myopic patients implanted with Artisan iris-fixated PIOLs (Ophtec BV) and 30 eyes of 15 myopic controls were enrolled. Corneal ECD and the distance between endothelium and the PIOL optic were evaluated in five different regions (central, nasal, superior, temporal, and inferior) using noncontact specular microscopy and rotating Scheimpflug imaging.

RESULTS: In PIOL-implanted patients, significant differences between the ECD in the superior region, compared with the lowest ECD in any region, and the ECD of the central region, compared with that of the region with highest ECD, were evident. When PIOL-implanted eyes were divided based on time since operation, a significant difference was observed only in patients for whom at least 48 postoperative months had elapsed. In untreated myopic controls, the greatest ECD was observed at the superior cornea. The distance between the central corneal endothelium and PIOL was significantly longer than that of the peripheral locations.

CONCLUSIONS: The extent of ECD decrease was not consistent throughout the cornea after implantation of an iris-fixated PIOL. Therefore, ECD measurement not only at the corneal center but also at midperipheral corneal locations, especially in the superior cornea, may be important in patients with iris-fixated PIOLs. [J Refract Surg. 2011;27(12):881-886.] doi:10.3928/1081597X-20110802-03

Currently, laser refractive surgery, including photorefractive keratectomy, LASIK, and laser epithelial keratomileusis, is commonly used to correct refractive errors. However, in patients with high refractive errors, these corneal reshaping procedures have limited efficacy, such as poor refractive predictability, prolonged visual recovery, instability of refraction, night vision disturbance, increased corneal higher order aberrations, risk of corneal scarring or progressive ectasia, and dry eye.1-3

Phakic intraocular lenses (PIOLs) for correcting high myopia were introduced in the 1950s by Strampelli4 and Barraquer.5 In 1986, Fechner and Worst began to implant iris-fixated PIOLs in phakic myopic eyes.6 Multicenter clinical studies have demonstrated that such PIOLs are safe and efficacious.7,8 Nevertheless, several studies have examined changes in corneal endothelial cell density (ECD) after implantation of iris-fixated PIOLs. During short-term follow-up, most studies have not found significant endothelial cell loss.9,10 Such losses have been reported in long-term studies, with at least 3 to 4 years of follow-up.11-13 However, all previous reports evaluated corneal endothelium cell numbers only at the corneal center; to date, the peripheral corneal endothelium has not been examined. Hence, using noncontact specular microscopy in the present study, we evaluated central and midperipheral
corneal ECDs of patients in whom iris-fixated PIOLs had been implanted >1 year prior to the study.

PATIENTS AND METHODS

PATIENT POPULATION

Forty-five eyes of 25 myopic patients implanted with a rigid Artisan iris-fixated PIOL (Ophtec BV, Groningen, The Netherlands) >1 year prior to the study and 30 age- and gender-matched eyes of 15 myopic individuals who had not received lens implantation (control group) were evaluated. Preoperatively, a patient with any of the following features had been considered unsuitable for iris-fixated PIOL implantation: central ECD ≤2000 cells/mm², anterior chamber depth (between the corneal endothelium and central anterior lens capsule) ≤3.2 mm, chronic systemic disease, history of ocular surgery, glaucoma, chronic uveitis, and preexisting ocular pathologic features or abnormality. Enrolled control myopic eyes had corrected distance visual acuity of 20/20 and no ocular abnormality other than refractive error.

IRIS-FIXATED PHAKIC INTRAOCULAR LENS IMPLANTATION

Surgery was performed using subtenon anesthesia with 2% lidocaine. A 6-mm diameter optic Artisan iris-fixated PIOL was inserted through a superior 6.2- to 6.3-mm corneoscleral incision in all patients. The power of the PIOL was chosen to achieve emmetropia. A two-plane corneoscleral incision was centered at 12 o’clock. Two stab incisions were performed at 2 o’clock and 10 o’clock; these were directed towards the enclavation sites. After intracameral injection of acetylcholine and insertion of a viscoelastic substance, the lens was introduced using a Budo forceps (Duckworth and Kent, Baldock, United Kingdom). After subtle rotation, the lens was fixated in the horizontal axis using a disposable enclavation needle (Ophtec BV). The viscoelastic substance was replaced with balanced salt solution (Alcon Laboratories Inc, Ft Worth, Texas). The wound was sutured with five interrupted 10-0 nylon sutures. Nd:YAG laser iridotomy was performed at 11 o’clock, to prevent development of pupillary-block glaucoma, 2 weeks before surgery. After each operation, topical 0.5% levofloxacin (Cravit; Santen, Osaka, Japan) and 1% prednisolone acetate (PredForte; Allergan, Irvine, California) were applied four times daily for 4 weeks and subsequently tapered. Selective suture removal was performed, depending on subjective refraction.

EVALUATION OF CORNEAL ENDOTHELIAL CELLS

We examined the corneal endothelium and obtained measures of ECD, coefficient of variation (CV), and hexagonality in the central zone and four midperipheral regions (nasally, superiorly, temporally, and inferiorly 3 mm away from the center of the cornea) using noncontact specular microscopy (SP 3000P; Topcon, Tokyo, Japan). Preoperatively, three endothelial cell measurements were obtained in only the central area. Finally, measurements were obtained in five examined areas were compared using one-way analysis of variance (ANOVA) with Bonferroni post-hoc comparison. The PIOL-implanted eyes were divided into four groups based on time since operation, and mean ECD values in five corneal areas were compared among these groups using one-way ANOVA with Bonferroni post-hoc comparison.

ROTTING SCHEIMPFLUG IMAGING

Rotating Scheimpflug imaging (Pentacam; Oculus Optikgeräte GmbH, Wetzlar, Germany) was performed in eyes with Artisan iris-fixated PIOLs to measure the complete cornea and anterior chamber. The distance between the central corneal endothelium and anterior optic side of the PIOL was measured using the Scheimpflug digital image. In addition, the distances between the endothelium and edge of the PIOL at four midperipheral regions (nasally, superiorly, temporally, and inferiorly) were analyzed using vertically or horizontally scanned images. Mean distances at the five areas were compared using one-way ANOVA with Bonferroni post-hoc comparison.

STATISTICAL ANALYSIS

Statistical analysis was performed using Statistical
RESULTS

Patient demographics are shown in Table 1. Mean power of the Artisan PIOLs was −11.80±2.70 diopters (D) (range: 6.50 to −15.00 D). In control individuals, mean refractive spherical equivalent refraction was −6.71±2.70 D (range: −4.00 to −8.50 D). The mean elapsed time after PIOL implantation was 40.7±18.9 months (range: 22 to 53 months), and all eyes had received PIOLs no less than 12 months prior to our study. All corneas were clear.

The mean ECD of eyes with PIOLs was highest at the corneal center and lowest in the superior peripheral area (Table 2). The mean ECD differed significantly among the five examined corneal areas, and a statistically significant difference compared to the corneal center measurement was observed in only the superior midperipheral area (Fig A). No significant differences in CV or hexagonality were found among the five corneal areas in eyes with PIOLs.

Differences among the ECD of the five corneal areas were also statistically significant in control eyes (Table 3). However, the mean ECD of the superior midperipheral area was the greatest, and significantly higher than that of the central cornea, temporal area, or inferior area (Fig B). No significant differences in CV or hexagonality were found among the five corneal areas in control myopic eyes, as was also noted for PIOL-implanted eyes.

The characteristics and mean ECD values at the five tested corneal areas of the four PIOL implantation groups, divided by time since operation, are listed in Table 4. The difference among the ECDs of the five corneal areas was statistically significant only in the group

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**Table 2**

<table>
<thead>
<tr>
<th>Region</th>
<th>Mean ECD (cells/mm²)</th>
<th>Mean CV</th>
<th>Mean Hexagonality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central</td>
<td>2763.7±309.0</td>
<td>52.9±30.4</td>
<td>48.3±14.9</td>
</tr>
<tr>
<td>Nasal</td>
<td>2694.8±376.2</td>
<td>54.1±32.9</td>
<td>50.2±14.4</td>
</tr>
<tr>
<td>Superior</td>
<td>2551.6±362.5</td>
<td>53.5±28.8</td>
<td>45.9±17.6</td>
</tr>
<tr>
<td>Temporal</td>
<td>2630.8±347.5</td>
<td>54.7±27.7</td>
<td>46.5±16.8</td>
</tr>
<tr>
<td>Inferior</td>
<td>2758.4±348.8</td>
<td>53.7±29.2</td>
<td>48.4±16.3</td>
</tr>
<tr>
<td><em>P value</em></td>
<td>.02</td>
<td>.99</td>
<td>.74</td>
</tr>
</tbody>
</table>

*PIOL = phakic intraocular lens, ECD = endothelial cell density, CV = coefficient of variation
*One-way analysis of variance.

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Figure. Mean endothelial cell density (ECD) in five corneal regions of A) Artisan iris-fixated phakic intraocular lens (PIOL) implanted eyes and B) control myopic eyes. In the eyes with PIOLs, superior corneal ECD was lowest, and a significant difference was observed between ECD of the superior cornea and that of the central cornea. In control eyes, superior corneal ECD was greatest, and significant differences were evident between the superior cornea and central, temporal, and inferior cornea, respectively. Error bars represent 2 standard deviations.
on whom operations had been performed >48 months before the time of examination. In this group, the region with the highest mean ECD was the central cornea, and the mean ECD of the superior corneal region was the lowest. A statistically significant difference in mean ECD of this group was observed between the superior and central ($P = .011$) or inferior area ($P = .014$).

The mean distance between the central corneal endothelium and anterior surface of the PIOL was significantly greater than the distance between the endothelium and optic edge of the PIOL at the four peripheral areas (Table 5). No statistically significant difference was noted in mean distance between the endothelium and edge of the PIOL among the four peripheral regions.

**DISCUSSION**

We sought to evaluate the central and peripheral (nasal, superior, temporal, and inferior) corneal endothelium of eyes implanted with Artisan iris-fixated PIOLs to correct high myopia. With iris-fixated PIOLs, the shortest distance of endothelium-IOL may be at the periphery of the optic, where the negatively powered lens is thickest. Thus, peripheral corneal endothelial

### TABLE 3

**Endothelial Cell Parameters in the Central and Four Midperipheral Regions of Myopic Control Eyes**

<table>
<thead>
<tr>
<th>Region</th>
<th>Mean ECD (cells/mm$^2$)</th>
<th>Mean CV</th>
<th>Mean Hexagonality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central</td>
<td>2874.5±273.7</td>
<td>55.4±28.5</td>
<td>48.9±14.4</td>
</tr>
<tr>
<td>Nasal</td>
<td>3081.7±259.2</td>
<td>59.1±30.1</td>
<td>48.9±13.0</td>
</tr>
<tr>
<td>Superior</td>
<td>3221.1±306.4</td>
<td>62.5±31.7</td>
<td>46.2±14.8</td>
</tr>
<tr>
<td>Temporal</td>
<td>2941.6±384.7</td>
<td>70.3±37.8</td>
<td>46.8±16.8</td>
</tr>
<tr>
<td>Inferior</td>
<td>2869.9±248.5</td>
<td>61.9±35.6</td>
<td>46.5±17.2</td>
</tr>
</tbody>
</table>

$P$ value*<.001 .50 .92

ECD = endothelial cell density, CV = coefficient of variation

*One-way analysis of variance.

### TABLE 4

**Characteristics of and Mean Endothelial Cell Densities in the Central and Four Midperipheral Regions of Artisan Iris-fixated PIOL-implanted Eyes**

<table>
<thead>
<tr>
<th>Time Since Artisan Iris-fixated PIOL Implantation</th>
<th>&lt;24 Months</th>
<th>24 to 36 Months</th>
<th>36 to 48 Months</th>
<th>&gt;48 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (eyes)</td>
<td>6 (10)</td>
<td>5 (10)</td>
<td>6 (10)</td>
<td>8 (15)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>3/3</td>
<td>2/3</td>
<td>1/5</td>
<td>3/5</td>
</tr>
<tr>
<td>Mean age (y)</td>
<td>32.4±9.7</td>
<td>32.4±7.5</td>
<td>33.2±9.5</td>
<td>32.1±3.2</td>
</tr>
<tr>
<td>Mean PIOL power (D)</td>
<td>−11.70±2.00</td>
<td>−10.30±1.30</td>
<td>−11.60±2.40</td>
<td>−12.60±3.50</td>
</tr>
<tr>
<td>Mean time since implantation (mo)</td>
<td>16.8±6.5</td>
<td>32.2±2.5</td>
<td>39.5±2.1</td>
<td>63.1±9.4</td>
</tr>
<tr>
<td>Mean ECD (cells/mm$^2$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central zone</td>
<td>2920.9±254.2</td>
<td>2545.6±384.7</td>
<td>2784.9±342.8</td>
<td>2790.2±187.4</td>
</tr>
<tr>
<td>Nasal zone</td>
<td>2925.5±335.9</td>
<td>2566.2±424.0</td>
<td>2846.2±353.4</td>
<td>2525.7±282.2</td>
</tr>
<tr>
<td>Superior zone</td>
<td>2656.3±303.9</td>
<td>2421.4±412.2</td>
<td>2713.2±368.4</td>
<td>2460.8±331.3</td>
</tr>
<tr>
<td>Temporal zone</td>
<td>2769.1±269.0</td>
<td>2549.4±384.9</td>
<td>2671.2±491.4</td>
<td>2566.1±241.9</td>
</tr>
<tr>
<td>Inferior zone</td>
<td>2845.4±291.2</td>
<td>2457.9±430.3</td>
<td>2939.0±278.3</td>
<td>2780.4±255.3</td>
</tr>
</tbody>
</table>

$P$ value* .21 .91 .52 .001

PIOL = phakic intraocular lens, ECD = endothelial cell density

*One-way analysis of variance.
cell loss is expected to be more pronounced than that to the central cornea. However, no report has separately evaluated changes to the central and peripheral corneal endothelium.

In the present study, the mean corneal ECD of eyes with PIOLs was highest at the center of the cornea and lowest in the region superior to the cornea. The difference of ECD between the superior area and central area was statistically significant. In normal human corneas, it has been shown that peripheral ECD is significantly higher than central ECD. In particular, superior peripheral ECD was reported to be significantly greater than ECD in other corneal regions. As the regional corneal ECD distribution differed between PIOL-implanted and normal eyes, we tried to verify endothelial parameters of control myopic eyes. Although our controls had a lower refractive spherical equivalent than the PIOL-implanted patients, we found that the mean ECD of the superior corneal area was significantly highest, as found in previous studies on normal corneas. The results indicate that the significantly lower ECD in the superior regions of Artisan iris-fixated PIOL-implanted eyes (compared with normal or control individuals) was caused by implantation of the Artisan PIOL.

The prominent decrease in superior corneal ECD may be attributed to the fact that the corneoscleral tunnel incision created for implantation of an iris-fixated PIOL is located in the superior region. During implantation, the superior corneal endothelium may be mechanically damaged by the surgical instruments employed and by creation of the corneoscleral tunnel. Additionally, the preoperative Nd:YAG laser iridotomies (performed at 11 o’clock) may have induced loss of superior corneal endothelial cells. In fact, Wu et al showed significant endothelial cell loss after Nd:YAG laser iridotomy at 1-year follow-up.

When we analyzed regional corneal ECDs in patients divided into groups based on time since implantation, no significant difference among ECDs of the five corneal regions tested was evident in the groups on whom operations had been performed less than 48 months earlier. It may be because corneal endothelial injury would be repaired by endothelial cell migration or other endothelial compensatory mechanisms. It is well known that human corneal endothelial cells compensate for cell loss by migration and cell enlargement, rather than by proliferation. In the group on whom operations had been performed more than 48 months earlier, the mean ECD of the central cornea was the highest, implying that midperipheral corneal endothelial cells suffer chronic long-term damage.

Vulnerability of the corneal periphery in the region of endothelium-PIOL contact can be marked. Doors et al reported that endothelial cell loss after PIOL implantation was associated with the distance from the edge of the PIOL to the corneal endothelium. We verified that the distances between the optic edge of the PIOL and corneal endothelium at four peripheral areas were significantly shorter than the distance between the central optic PIOL and endothelium. Also, we found that the ECDs in peripheral corneal regions were lower than that of the central cornea, although no statistically significant difference among the mean ECD of the corneal center and three midperipheral corneal areas was apparent except for the superior region in Artisan PIOL implanted eyes. On the other hand, the lowest ECD was at the corneal center in control myopic eyes. These results show that the short distance between the optic edge and corneal endothelium may be a reason for peripheral endothelial cell loss. Hence, we believe that the prominent loss of superior corneal ECD is associated with both mechanical damage during the PIOL implantation procedure and the proximity of the optic edge to the peripheral corneal endothelium. To validate this possibility, PIOL implantation through incisions other than superior would be necessary.

Although we did not compare regional corneal endothelial changes before and after PIOL implantation because of the lack of preoperative regional endo-

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### TABLE 5

| Intraocular Distance Between the Corneal Endothelium and PIOL Optic Analyzed With Rotating Scheimpflug Imaging in the Central and Four Midperipheral Areas of Eyes With Artisan Iris-fixated PIOLs |

<table>
<thead>
<tr>
<th>Midperipheral Areas</th>
<th>Mean distance (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Central Area</td>
</tr>
<tr>
<td>Mean distance (µm)</td>
<td>2210.0±207.6*</td>
</tr>
</tbody>
</table>

PIOL = phakic intraocular lens
*The distance was significantly longer than the other distances at the four peripheral areas (P<.001, one-way analysis of variance with Bonferroni post-hoc comparison).
Corneal endothelial data, we found that the extent of ECD loss was not consistent over the entire cornea after implantation of an Artisan iris-fixated PIOL. The lens seemed to cause a greater decrease of ECD in the midperiphery, especially superiorly, approximately 4 years after implantation. Therefore, we suggest that measurement of ECD not only at the center of the cornea, but also at midperipheral corneal regions, especially the superior area, may be beneficial if performed preoperatively and during follow-up after iris-fixated PIOL implantation, thereby detecting rare cases of severe loss of corneal endothelial cells in advance and the proper time for PIOL explantation.

**AUTHOR CONTRIBUTIONS**

- Study concept and design (B.J.C., T.K.);
- Data collection (B.J.C., H.R., E.K.K.);
- Analysis and interpretation of data (J.H.K.);
- Drafting of the manuscript (J.H.K., H.R.);
- Critical revision of the manuscript (B.J.C., E.K.K., T.K.)

**REFERENCES**


