Model to Predict Endothelial Cell Loss after Iris-Fixated Phakic Intraocular Lens Implantation

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PURPOSE. To describe a model predicting endothelial cell (EC) loss after iris-fixated phakic intraocular lens (pIOL) implantation, taking distance from the edge of the pIOL to the corneal endothelium into account.

METHODS. This prospective observational study monitored long-term EC changes in 306 eyes after pIOL implantation. EC density (ECD) was determined before surgery, 6 months after surgery, and then annually up to 8 years after surgery. Mean follow-up was 31.7 ± 25.7 months. All eyes underwent anterior segment optical coherence tomography to determine minimum distance from the edge of the pIOL to the corneal endothelium. Linear mixed-model analysis was performed to present a model that describes EC loss as a linear decrease and an additional decrease depending on the minimum distance of the pIOL to the endothelium. The main purpose was to design a model that can help physicians during patient selection and follow-up process. It might be used to predict when a patient will reach a critical endothelial cell density level, such as an ECD of 1500 cells/mm², at which point, in our opinion, pIOL explantation and cataract extraction can still safely be performed.

RESULTS. Mean minimum edge distance was 1.43 ± 0.23 mm (range, 0.70–2.21 mm). For this mean edge distance, the model predicted a yearly EC loss of 1.0%, whereas an edge distance of 1.20 mm resulted in a yearly EC loss of 1.7%, and an edge distance of 1.66 mm led to a yearly EC loss of 0.2%. Furthermore, the model predicted that for patients with preoperative ECDs of 3000, 2500 or 2000 cells/mm², and edge distances of 1.43 mm, a critical ECD of 1500 cells/mm² (at which point pIOL explantation and cataract extraction can still safely be performed) will be reached at 56, 37, and 18 years after implantation.

CONCLUSIONS. The presented model predicts EC loss after iris-fixated pIOL implantation in relation to the measured edge distance, patient age, and preoperative ECD, which can assist ophthalmologists in patient selection and follow-up of pIOLs.

Invest Ophthalmol Vis Sci. 2010;51:811–815 DOI:10.1167/iovs.09-3981

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Since 1991, iris-fixated phakic intraocular lenses (pIOLs) have been successfully implanted in healthy eyes to correct myopia, hyperopia, and astigmatism. Previous studies have demonstrated that these pIOLs show stable and predictable visual results when strict inclusion criteria for implantation are applied. However, long-term endothelial cell (EC) loss remains a point of discussion. To investigate the effect of iris-fixated pIOLs on the corneal endothelium, several clinical trials studied EC loss after pIOL implantation, with variable results. Some investigators reported no statistically significant EC loss, whereas others found highly significant EC losses continuing up to 5 years after pIOL implantation (9.0% at 5 years postoperatively). Furthermore, Saxena et al. reported a significant 12.6% EC loss 7 years after pIOL implantation and a significant negative correlation between anterior chamber depth (ACD) and EC loss after 3 years.

New noncontact imaging techniques have been extremely valuable in guaranteeing a safe distance from the pIOL to critical ocular tissues. Anterior segment optical coherence tomography (AS-OCT) has proven to be a good imaging tool to visualize the pIOL in the anterior chamber and to analyze its distance from the corneal endothelium and the crystalline lens. This has led to the development of new criteria to warrant the long-term safety of pIOLs. One of the mentioned criteria is a minimum distance from the edge of the pIOL to the corneal endothelium, which is the smallest distance (1.5 mm) from the pIOL to the endothelium because of its convex-concave shape. A new software update (Visante AS-OCT; Carl Zeiss Meditec Inc., Dublin, CA) has the ability to perform pIOL simulation and, consequently, can measure edge distance before surgery.

Recently, the importance of this edge distance has been demonstrated by Doors et al. They found that EC loss after pIOL implantation was associated with the distance from the edge of the pIOL to the corneal endothelium. An edge distance of 1.37 mm resulted in a yearly EC loss of 0.98%, whereas an edge distance of 1.15 mm predicted a yearly loss of 1.8%. Furthermore, the edge distance might not be constant with advancing age. Age-related changes to the crystalline lens cause a decrease in ACD of approximately 20 μm per year. Guell et al. reported a stable distance between the pIOL and the crystalline lens during accommodation, which might suggest that the iris and the crystalline lens act as a unit and move forward. Consequently, if the iris and the crystalline lens move forward with an iris-fixated pIOL, the distance from the edges of the pIOL to the endothelium might decrease with increasing patient age.

In this study, we have extended our previous observations to an increased number of patients and assessed whether the endothelial cell density (ECD) changes conform to a mathematical model, taking the relationship between EC loss and edge distance into account. The main purpose was to design a model that can help physicians during the patient selection and follow-up process. It might be used to predict when a patient will reach a critical endothelial cell density level, such as an ECD of 1500 cells/mm², at which point, in our opinion, pIOL explantation and cataract extraction can still safely be performed. To help ophthalmologists in patient selection, the model might be used to predict how long the pIOL can remain safely in the eye using the preoperative edge distance, measured with the pIOL simulation program (Visante AS-OCT; Carl Zeiss Meditec Inc.), and the preoperative ECD count.

METHODS

This prospective observational study included 306 consecutive eyes of 162 patients, who underwent pIOL implantation with Artisan or Arti-
The Artisan pIOL (Ophtec B.V.) is a rigid single-piece lens composed of polymethyl methacrylate (PMMA). It has a convex-concave shape with either a 6-mm (for intraocular lens powers up to −15.5 diopters [D]) or 5-mm (for intraocular lens powers from −16.0 to −24.0 D) optic. In contrast, the foldable Artiflex pIOL (Ophtec B.V.) is a three-piece lens that consists of a flexible optical part made of ultraviolet-absorbing silicone and two rigid haptics made of PMMA. Because of its foldable 6-mm silicone optic, this lens can be inserted through a smaller incision. The Artiflex pIOL is available in dioptic powers of −2.0 to −14.5. The surgical procedures were performed by the same surgeon (RN). The surgical technique of pIOL implantation and postoperative eyedrops regimen has been described elsewhere.10,16 The incidence size for implantation of the rigid Artisan pIOL was 6.2 or 5.2 mm, depending on the size of the optic. For the foldable Artiflex pIOL, a 3.2-mm incision was used. The criteria for performing pIOL implantation in our institution are stable refractive error during the previous 2 years; central ACD of 2.8 mm or more (measured from the endothelium to the crystalline lens); pupil (in mesopic light conditions) <6 mm; endothelial cell density ≥2000 cells/mm²; no corneal, pupil, or iris abnormalities; and no history of glaucoma or chronic or recurrent uveitis.

Before surgery, central ECD measurements were performed using a noncontact specular microscope (Noncon Robo SP-8000; Konan Medical Inc., Hyogo, Japan) and were repeated at 3 and 6 months and at 1, 2, 3, 4, 5, 6, 7, and 8 years after surgery. Follow-up ranged from 3 months to 8 years, with a mean follow-up of 31.7 ± 25.7 months per eye. Three consecutive endothelial images of the central cornea were obtained and analyzed using the dot method, in which the centers of 50 or more contiguous cells are marked. The average of these three measurements was used for the analysis. EC loss was defined as the decrease in cell density between the preoperative and postoperative examination expressed as a percentage of the preoperative cell density. Paired t tests were used to compare preoperative EC counts with postoperative EC counts for each follow-up visit. To correct for the multiple tests, we used a Bonferroni correction, which meant that a P < 0.009 was considered significant for the conducted paired t-tests (Table 1). During all follow-up examinations, patients were examined to detect complications, such as glaucoma or corneal edema.

From 2006 to 2008, AS-OCT was performed once in all included patients to analyze the position of the iris-fixated pIOL using an OCT system (Visante; Carl Zeiss Meditec Inc.). All AS-OCT images were made on the horizontal meridian, in an unaccommodated state, and in the same light conditions (50 lux). Cross-sectional images were taken using the enhanced anterior segment single scan. One examiner analyzed the images and measured the distances from the edges of the pIOL to the corneal endothelium using the refractive tools provided by the manufacturer (Fig. 1). Of the two edge distances (nasal and temporal side), the smallest distance was used for statistical analysis.

Linear mixed-model analysis was applied to our data, with ECD as an independent variable and time as a covariate and assuming a random intercept per eye. This linear model is a useful test because it uses all available ECD data for each patient to fit the best linear model. To look for possible differences in EC loss for pIOLs with different distances between the edge of the pIOL and the corneal endothelium, we also included an interaction term “time” × “edge pIOL-corneal endothelium distance.” Our approach was to fit a linear mixed model using the following equation:

![Figure 1. Anterior segment optical coherence tomography scan showing measured edge distances on the nasal (1.44 mm) and temporal (1.58 mm) side.](image-url)
and a mean preoperative ECD count of 2624 cells/mm². Artisan pIOLs showed a mean edge distance of 1.48 mm and 1.43 mm (range, 0.70–2.21 mm). The mean preoperative ECD count was 2693 cells/mm² and edge distances of 1.20 mm (i.e., mean edge distance 0.23 mm) resulted in a yearly EC loss of 1.7%, and an edge distance of 1.66 mm led to a yearly EC loss of only 0.2%.

For patients with preoperative ECDs of 3000, 2500, or 2000 cells/mm² and edge distances of 1.43 mm, the model predicted that a critical ECD of 1500 cells/mm² will be reached at 56, 37, and 18 years after implantation, respectively.

### DISCUSSION

In this study, we analyzed the data of 306 eyes after iris-fixated pIOL implantation and computed a linear mixed model to predict long-term EC loss in relation to the distance from the edge of the pIOL to the corneal endothelium. To our knowledge, this is the first attempt to describe such a model for patients after pIOL implantation. In the past, models predicting EC loss after cataract surgery and penetrating keratoplasty (PK) have been presented using exponential decay models.17–19

**TABLE 2.** Parameter Estimates of Linear Mixed-Model Analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (cells/mm²) ± SE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept α</td>
<td>2693 ± 18.5</td>
<td>2656–2729</td>
</tr>
<tr>
<td>Effect of time β</td>
<td>-12.95 ± 1.58</td>
<td>-16.05–9.85</td>
</tr>
<tr>
<td>Interaction effect γ</td>
<td>7.51 ± 1.06</td>
<td>5.44–9.58</td>
</tr>
</tbody>
</table>

\[ y_{i}(t,d) = \alpha + \alpha_i + \beta t + \gamma(t,d) + e_i \]  

(1)

where \( y_{i}(t,d) \) is the ECD count of an eye \( i \) after a follow-up of \( t \) months with edge distance \( d \); \( \alpha \) represents the intercept; \( \alpha_i \) represents the random intercept per eye; \( \beta \) is the effect of time after a follow-up of \( t \) months; \( \gamma \) is the interaction effect of time and edge distance with edge distance \( d \) and a follow-up of \( t \) months; and \( e_i \) is the residual error.

**RESULTS**

Of the 306 included eyes, 186 eyes received an Artisan Myopia pIOL with a mean lens power of -12.91 ± 3.79 D (range, -5.00 to -23.50 D), 15 eyes were implanted with an Artisan Toric pIOL with a mean lens power of -7.77 ± 4.04 D (range, -2.00 to -15.00 D), 99 eyes received an Artiflex Toric pIOL with a mean lens power of -10.06 ± 2.25 D (range, -4.00 to -14.50 D), and 6 eyes received an Artiflex Toric pIOL with a mean lens power of -8.33 ± 3.32 D (range, -5.00 to -10.50 D). The mean preoperative ECD count was 2693 ± 547 cells/mm² (range, 1588–3753 cells/mm²), and the mean minimum edge distance was 1.45 ± 0.23 mm (range, 0.70–2.21 mm). Artisan pIOLs showed a mean edge distance of 1.48 ± 0.23 mm and a mean preoperative ECD count of 2624 ± 355 cells/mm². The mean edge distance of the Artiflex pIOLs was 1.32 ± 0.20 mm, and the mean preoperative ECD count was 2775 ± 310 cells/mm². Eleven patients included in this study wanted the pIOL implantation despite an ECD exceeding 3000 cells/mm², and our warnings about possible complications; ECD in most of the patients (n = 8) was between 1950 and 2000 cells/mm². They underwent implantation because of complete contact lens intolerance and the inability to continue their occupations with spectacle correction. Mean EC losses at 6 months and 1 year after pIOL implantation were 0.40% ± 9.85% and 1.23% ± 9.52%, respectively. To illustrate the ECD data used to compute the model, the changes in ECD at each follow-up visit compared with before surgery are shown in Table 1. All corneas of the included eyes stayed clear during follow-up.

Estimated parameters of the linear mixed model are listed in Table 2. When using these estimates in the described model, the following equation can be computed:

\[ y_{i}(t,d) = 2693 + \alpha_i - 12.95 t + 7.51 td + e_i \]  

(2)

When applying this model to a patient with a preoperative ECD count of 2693 cells/mm² (i.e., mean ECD count of the investigated population) and a minimum edge distance of 1.43 mm (i.e., mean edge distance of the investigated population), the predicted ECD at 5 years after surgery would be \( y(60,1.43) = 2693 - 12.95 	imes 60 + 7.51 	imes (60 	imes 1.43) = 2560 \) cells/mm². We can also calculate that after 44 years the patient will have enough endothelial cells (1525 cells/mm²)14,15 to undergo pIOL explantation and cataract extraction (Figs. 2, 3). The predictions of minimum edge distances of 1.66 mm and 1.20 mm (i.e., mean edge distance ± 1 SD) in the same patient are also shown in Figure 2 with the corresponding years of reaching ECD counts of 1500 cells/mm² in Table 3. For the mean edge distance of 1.43 mm, the model predicted a yearly EC loss of 1.0%, whereas an edge distance of 1.20 mm resulted in a yearly EC loss of 1.7%, and an edge distance of 1.66 mm led to a yearly EC loss of only 0.2%.

For patients with preoperative ECDs of 3000, 2500, or 2000 cells/mm² and edge distances of 1.43 mm, the model predicted that a critical ECD of 1500 cells/mm² will be reached at 56, 37, and 18 years after implantation, respectively.

**FIGURE 2.** Linear mixed model applied to patient eligible for pIOL implantation with preoperative endothelial cell count of 2693 cells/mm² and edge distances of 1.20 mm (half dotted line), 1.43 mm (straight line), and 1.66 mm (dotted line).

**FIGURE 3.** Linear mixed model applied to patient eligible for pIOL implantation with preoperative endothelial cell count of 2693 cells/mm² and edge distance of 1.43 mm (straight line) with the confidence intervals of the model (dotted line).
operative period. We used a single linear model because it offers an exponential decrease with a rapid linear decrease in the early postoperative period. We used a single linear model because it offers a better fit to our data. Our EC loss results showed that we did not find a large EC loss shortly after pIOL implantation, which is the case after cataract surgery and penetrating keratoplasty and thus follows an exponential decay model. An explanation for this stable ECD in the first months after pIOL implantation might be the redistribution of endothelial cells from the periphery to the center after the discontinuation of contact lens wear. Peripheral corneal ECD seems to be significantly higher than central corneal ECD and functions as a physiologic reserve for endothelial cells. Similar to our results, most studies investigating EC loss after pIOL implantation did not report a rapid loss in the first 6 months after surgery. In these studies, short-term EC losses varied from 0.09% at 6 months to 3.3% at 1 year after surgery. Our reported mean EC losses of 4.3% at 5 years and 5.4% at 7 years after pIOL implantation are in accordance with the recent literature. Three years after pIOL implantation, Stulting et al. reported an EC loss of 4.8%, and Benedetti et al. found an EC loss of 9.0% at 5 years after surgery.

The aim of our study was to describe a model to assist opthalmologists in their decision to implant iris-fixated pIOLs into healthy eyes. The presented model uses preoperative ECD and the minimum edge distance to estimate ECD counts during follow-up. To build the described model, the edge distance was measured postoperatively because AS-OCT has only been available in our institution since 2006. A new software update of the OCT (Visante; Carl Zeiss Meditec Inc.) system now has the possibility to assess the edge distance in the preoperative setting using a pIOL simulation program. Recently, we tested this pIOL simulation tool and found small mean differences between preoperative simulation and actual postoperative measurements. Therefore, this preoperative simulation is a useful tool in determining edge distance in the preoperative patient, which can be used in the presented model.

However, as we mentioned before, it is known that ACD decreases with age, which might result in a decrease in the minimum edge distance over time. In our opinion, all patients should be monitored using AS-OCT during long-term follow-up to investigate the effect of age on the minimum edge distance. For example, when presuming a yearly ACD decrease of 20 μm, which, in a worst-case scenario, will result in a decreasing edge distance of 0.02 mm per year, the presented patient with a preoperative ECD count of 2693 cells/mm² and a minimum edge distance of 1.43 mm, will reach an ECD count of 1500 cells/mm² 42 years after pIOL implantation (Fig. 4). This is 2 years sooner than predicted without taking this decrease of ACD into account. As more data become available during long-term follow-up of pIOLs using AS-OCT, we hope this leads to the development of a good mathematical description of the postoperative EC loss with an accurate estimation of the decrease in edge distance over time.

We tried to evaluate our model using studies reporting EC loss after iris-fixated pIOL implantation. However, the main problem of previously reported studies was the unavailability of measured edge distances, which can be expected because the Visante OCT (Carl Zeiss Meditec Inc.) has only been on the market since 2006. Computing an estimated mean edge distance for all available data was difficult because edge distance is related to ACD but also to the power and design of the pIOL. Furthermore, some studies did not report mean ACD or did not describe the measurement device, which makes it difficult to assess whether ACD was measured from the crystalline lens to the endothelium or epithelium. Our suggestion would be to perform AS-OCT before surgery and to use the pIOL simulation program to estimate edge distance but also to continue the evaluation of this edge distance during long-term follow-up.

One of the limitations of a prediction model in general is the uncertainty of extrapolation of the data outside the ranges of the estimated values. The minimum edge distances of the eyes included in our study ranged between 0.70 and 2.21 mm. Therefore, in patients with minimum edge distances lower than 0.70 mm, the model should not be used since this could lead to inaccurate ECD estimates. Our maximum follow-up period was 8 years with a limited number of eyes. Therefore, extrapolation after our 8 years of follow-up could become more unreliable. We will continue to monitor our ECD data in the coming years and hope to provide more accurate values beyond 8 years of follow-up with a larger number of eyes in the future. Furthermore, to increase the validity of the presented model, it should be applied to a second independent population for validation. In our model we included both eyes of a large number of patients, which can cause bias in the statistical analysis. However, when repeating the analysis using only right or left eyes, the results were not very different from the presented model; therefore, we believe that the inclusion of both eyes did not lead to severe bias.

Our decrease in ECD is described as an absolute decrease in endothelial cells, which is actually a worst-case scenario. When using a relative decrease, which is usually reported in articles about EC loss, the decrease in ECD would be not as fast as the
absolute decrease. An example of a relative decrease is visualized for the presented patient in Figure 4. During the first 15 years of follow-up, the relative and absolute EC losses are almost identical. After this period, the difference between the models becomes evident. The patient will reach our critical ECD count of 1500 cells/mm² 70 years after implantation.

In conclusion, a linear mixed-model analysis was used to describe a linear model that predicts ECD counts after iris-fixed pIOL implantation in relation to the measured minimum edge distance using AS-OCT. Longer follow-up with AS-OCT will be needed to evaluate the effect of age-related changes of the natural lens on the distance from the edge of the pIOL to the endothelium.

References