Corneal Endothelial Cell Changes in Pseudoexfoliation Syndrome After Cataract Surgery

Christopher Wirbelauer, MD; Norbert Anders, MD; Duy T. Pham, MD; Josef Wollensak, MD

Objective: To characterize possible differences in endothelial cell changes after cataract surgery in patients with pseudoexfoliation syndrome (PSX).

Methods: In this prospective, age-matched, controlled clinical study, 25 consecutive patients with PSX and 25 control patients with senile cataracts only were studied. All patients were treated with standardized cataract surgery. Sequential quantitative and qualitative morphometric endothelial cell analyses of the central and para-central cornea were performed preoperatively and postoperatively at 1 day, 4 weeks, and 6 months using noncontact specular microscopy.

Results: Preoperative endothelial cell counts were 9.9% (P<.05) lower in patients with PSX (2387±266 cells/mm²) than in controls (2648±349 cells/mm²). The mean endothelial cell loss was 11.1% in the PSX group and 10.3% (P<.001 for both) in the control group, with no intergroup differences after 6 months. The mean endothelial cell area increased in both groups. Also, qualitative analysis revealed no significant differences in the endothelial repair mechanisms.

Conclusions: Endothelial cell density is reduced preoperatively in patients with PSX compared with age-matched controls. In patients with PSX, cataract surgery induced similar endothelial cell changes without increased endothelial cell loss postoperatively.


Corneal endothelial cell changes after cataract surgery in patients with pseudoexfoliation syndrome (PSX).

The corneal endothelium is essential for maintenance of normal corneal hydration, thickness, and transparency. This cellular monolayer is highly vulnerable and has only limited regenerative capacity. In patients with pseudoexfoliation syndrome (PSX), quantitative and qualitative morphological changes of the corneal endothelium have been demonstrated in specular and electron microscopic studies.1,4 It has been postulated that these changes represent an abnormal or unstable endothelium, predisposing to an endotheliopathy that may be more susceptible to the effects of intraocular surgery.1,5 The presence of PSX increases the incidence of intraoperative and postoperative complications during cataract surgery. Insufficient mydriasis and possible zonular instabilities can complicate the intraoperative course. Thus, higher corneal endothelial cell loss with impairment of the endothelial barrier and pump function can occur after intraocular manipulations.

This study sought to investigate the reactions of the corneal endothelium associated with cataract surgery in patients with PSX.

Table 1 summarizes important preoperative and intraoperative variables. Eight of the 25 patients with PSX previously underwent surgery on the nonexamined eye. Fourteen of the 17 patients for whom this was the first operation had bilateral involvement, and 3 were affected unilaterally. The semiquantitative analysis of PSX material on the anterior lens capsule revealed mild deposition in 4 (16%) patients, moderate in 18 (72%), and marked in 3 (12%). The pupillary dilatation was reduced in patients with PSX (Table 1).

The quantitative results of the corneal endothelium revealed preoperatively in the PSX group (mean±SD, 2387±266; range, 1886-2891 cells/mm²) a significant reduction of 9.9% (P=.02) total ECD compared with the control group (mean±SD, 2648±349; range, 2071-3190 cells/mm²) (Table 1). Also, regional morphometric data revealed reduced ECDs in central and paracentral areas in the PSX group compared with the control group (Table 2). Preoperative mean paracentral cell counts in the control group were 6.7% (178 cells/mm²) higher than central...
PATIENTS AND METHODS

PATIENTS AND CLINICAL EXAMINATION

Twenty-five consecutive patients with clinically diagnosed PSX were studied prospectively in a controlled clinical setting. Each patient underwent a complete preoperative opthalmologic examination, including anterior segment biomicroscopy, Goldmann applanation tonometry, gonioscopy, and binocular ophthalmoscopy. The diagnosis of PSX was made with the patient in mydriasis with the typical biomicroscopic findings of the presence of white grayish exfoliation material on the anterior lens capsule and/or the pupillary margin. The amount of PSX material on the anterior lens capsule was graded semi-quantitatively (score: +, mild; ++, moderate; +++ marked). Preoperative maximum mydriasis (2.5% phenylephrine hydrochloride, 1% tropicamide) was measured with standardized calipers. The control group consisted of 25 age-matched patients who had no ocular diseases other than senile cataracts and who were referred to our service for routine cataract surgery (Table 1). Preoperative normal intraocular pressure was an eligibility criterion. Patients showing evidence of any ocular or systemic disease associated with changes in the corneal endothelial structure were excluded from the study, and none of the patients had previous ocular surgery. Postoperative examinations were performed 1 day, 4 weeks, and 6 months after cataract extraction. All study patients had complete follow-up visits.

SURGICAL PROCEDURE

After informed consent was obtained, all patients underwent an identical standardized surgical procedure that included a self-sealing, trapezoidal, 7-mm scleral tunnel incision 2 mm from the limbus. The surgical approach depended on the preoperative astigmatism, resulting in a superior incision in patients with astigmatism with the rule (n=18) and a temporal incision in patients with astigmatism against the rule (n=7). After the circular continuous capsulorhexis maneuver, bimanual phacoemulsification in the posterior chamber was performed using the 4-quadrant, divide-and-conquer nucleofractis technique. The phaco-chop technique was preferred in patients with a hard nucleus. A posterior, nonheparinized, 1-piece polymethylmethacrylate intraocular lens was implanted in the capsular bag using sodium hyaluronate (Healon, Pharmacia, Uppsala, Sweden). At the end of the operation the viscoelastic was completely removed, and the conjunctiva was closed by bipolar cautery. An effort was made to use identical surgical techniques performed only by highly experienced surgeons in all patients. Topical corticosteroids and mydriatics were given from the first postoperative day. Eyedrops, 1% dexamethasone, were continued 3 times a day for 4 weeks.

ENDOTHELIAL MORPHOMETRY

The central and paracentral corneal endothelium was serially examined using a clinical, noncontact specular microscope (Konan Noncon Robo-ca SP 8000, Konan, Hyogo, Japan). Computerized image analysis was performed directly from video recordings of specular images of the endothelium combined with a frame grabber and an autofocus device, which focuses on the same area of the cornea. This microscope provides for rapid morphometric analysis and has high reproducibility and an accuracy comparable with that of contact methods.7 We performed sequential central and fixed paracentral specular imaging at each examination to analyze regional differences. The images from the paracentral cornea were taken in an area approximately midway between the center of the cornea and the limbus and in the direction in which the incision was positioned. During each recording, image quality and resolution were noted. Only high-contrast–focused endothelial images with sufficient quality for analysis were processed. If possible, specular microscopic images were taken on the first postoperative day. However, some early postoperative measurements were repeated 2 to 4 days after surgery because high-quality images could not be taken in some cases. All measurements were performed by the same experienced examiner (C.W.).

Subsequently, each endothelial image was studied with both incorporated computerized image analysis methods. To determine the endothelial cell density (ECD), the endothelial cells were counted in a manually determined rectangular frame with a constant area of 4.0 x 4.5 cm on the monitor (0.045 mm² on the corneal endothelium). All complete cells within the border of the rectangle and all partial cells intersecting 2 adjacent borders were marked.

Because endothelial cell counting alone is not sufficient for detecting subtle qualitative and functional changes in the endothelial monolayer, a cell analysis also was performed using the automatic center method algorithm.7 The center of adjacent cells were marked with a mouse and digitized. This permitted a determination of the ECD and mean cell area, thus describing the cell size. Using this algorithm, an immediate qualitative analysis of the morphological characteristics of the cell is possible. Polymegethism was assessed using the coefficient of variation of cell area, which is independent of cell area or density, and pleomorphism was assessed by the percentage of hexagonal cells.

To determine the ECD by the fixed frame method, a mean of 125 cells were sampled, and 130 cells were routinely digitized using the center cell analysis method. A second measurement had to be repeated in 64 (16%) of the determinations due to differences between both counting methods of more than 5% or 150 cells. Reevaluations were more frequent in the early postoperative period. The central and paracentral ECDs were calculated from the resulting mean of both counting methods. Total morphometric values were determined from central and paracentral variables.

STATISTICAL ANALYSIS

Any statistical differences noted between the 2 groups regarding age, intraocular pressure, pupil diameter, preoperative and postoperative endothelial cell variables, or ultrasound time and power were analyzed using the Mann-Whitney U test (intergroup differences). To compare sex distribution, the χ² test was used. Statistical differences with $P<.05$ were considered significant.

Changes in the individual groups were analyzed with the Wilcoxon signed rank test (intragroup differences). An α level of 5% was chosen for comparison. Bonferroni adjustment was made for multiple testing, and $P<.008$ was accepted as the significance level.
198 cells/mm²). This suggests a diffuse endothelial cell gions (11.8%; 324 cells/mm²) than in the center (7.7%; 222 cells/mm²) higher in the PSX group. Thus, differences in ECDs between both groups were higher in the paracentral re-

124 cells/mm²) in the control group (6.1% and 11.3% (P<.001 for both), respectively (Table 2). In the control group, endothelial cell loss was 6.1% in the center and 12.2% (P=.003 for both) in the para-

central regions (Table 2). The central cornea was more affected in the PSX group than in the control group, how-

ever, without intergroup differences.

Stabilization without further significant endothelial cell loss was observed during the remainder of follow-
up, with only modest regional differences between both groups (Table 2). The mean endothelial cell loss ranged in the central cornea from 7.7% to 10.8% and in the para-
central cornea from 11.4% to 12.4% after 6 months, without significant intergroup differences (Table 3).

Preoperatively, the total mean endothelial cell area was 40 µm² (P=.01) higher in the PSX group (Table 1). Due to compensatory enlargement of the cells, the mean endothelial cell area increased progressively centrally and paracentrally in the postoperative period (Table 2). The total increase in cell area was 70 µm² in the PSX group and 51 µm² in the control group (P<.001 for both) after 6 months, without intergroup differences.

The qualitative variables—polymegethism and pleomorphism—presented no preoperative differences in our

cell counts, whereas they were only 2.2% (52 cells/ mm²) higher in the PSX group. Thus, differences in ECDs between both groups were higher in the paracentral regions (11.8%; 324 cells/mm²) than in the center (7.7%; 198 cells/mm²). This suggests a diffuse endothelial cell reduction in both central and paracentral areas in pa-

tients with PSX. In patients with PSX without previous surgery on the other eye, the endothelial variables re-

vealed a similar pattern, with reduced total ECD com-
pared with controls (Table 1).

The mean (±SD) intraoperative ultrasound time (89±50 seconds) and power (38%±16%) did not differ be-

between groups (Table 1). A posterior capsular break with vitreous loss occurred in 1 patient with PSX. The intra-

ocular lens was implanted in the ciliary sulcus only in this patient. In all other patients there were no complications.

Within the first postoperative day, the ECD showed stabilization without further significant endothe-

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Table 1. Preoperative and Intraoperative Variables*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Group (n=25)</th>
<th>PSX Group (n=25)</th>
<th>PSX Other Eye (n=17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>77.1±6.5</td>
<td>78.0±8.8</td>
<td>77.8±9.3</td>
<td>.20†</td>
</tr>
<tr>
<td>Sex, F:M</td>
<td>15:10</td>
<td>18:7</td>
<td>13:4</td>
<td>.37‡</td>
</tr>
<tr>
<td>Intraocular pressure, mm Hg</td>
<td>16.5±3.1</td>
<td>16.6±3.2</td>
<td>16.6±3.2</td>
<td>.97†</td>
</tr>
<tr>
<td>Mydriasis, mm Hg</td>
<td>7.9±0.6</td>
<td>6.6±0.9</td>
<td>6.7±0.9</td>
<td>&lt;.001§</td>
</tr>
<tr>
<td>Total ECD, cells/mm²</td>
<td>2648±349</td>
<td>2387±266</td>
<td>2382±310</td>
<td>.02‡</td>
</tr>
<tr>
<td>Total mean cell area, µm²</td>
<td>383±50</td>
<td>424±48</td>
<td>425±56</td>
<td>.01‡</td>
</tr>
<tr>
<td>Total CV, /100</td>
<td>0.36±0.03</td>
<td>0.36±0.05</td>
<td>0.35±0.03</td>
<td>.83†</td>
</tr>
<tr>
<td>Total 6A, %</td>
<td>58.4±2.6</td>
<td>61.1±5.6</td>
<td>61.0a±5.8</td>
<td>.06†</td>
</tr>
<tr>
<td>Ultrasound</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, s</td>
<td>77±45</td>
<td>99±53</td>
<td>0</td>
<td>.14‡</td>
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<tr>
<td>Power, %</td>
<td>39±20</td>
<td>38±13</td>
<td>0</td>
<td>.77†</td>
</tr>
</tbody>
</table>

* Data are given as means±SD. Total values indicate the mean of central and paracentral parameters. PSX indicates pseudoexfoliation syndrome; PSX Other Eye, the eye that was not operated on in patients with PSX; ECD, endothelial cell density; CV, coefficient of variation of cell area; and 6A, percentage of hexagonal cells.
† Control group vs PSX group (Mann-Whitney U test).
‡ Control group vs PSX group (χ² test).

Table 2. Preoperative and Postoperative Endothelial Cell Variables*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Region of Cornea</th>
<th>Preoperative</th>
<th>1 d</th>
<th>4 wk</th>
<th>6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECD, cells/mm²</td>
<td>Central</td>
<td>2559±307</td>
<td>2361±245†</td>
<td>2396±339‡</td>
<td>2111±336‡</td>
</tr>
<tr>
<td>Paracentral</td>
<td>2737±440</td>
<td>2413±313†</td>
<td>2366±339‡</td>
<td>2132±396†</td>
<td>2341±487‡</td>
</tr>
<tr>
<td>Area, µm²</td>
<td>Central</td>
<td>394±50</td>
<td>428±64†</td>
<td>417±59</td>
<td>480±79†</td>
</tr>
<tr>
<td>Paracentral</td>
<td>372±56</td>
<td>419±55†</td>
<td>425±61‡</td>
<td>480±85†</td>
<td>452±129‡</td>
</tr>
<tr>
<td>CV, /100</td>
<td>Central</td>
<td>0.34±0.04</td>
<td>0.36±0.06</td>
<td>0.38±0.05</td>
<td>0.36±0.06</td>
</tr>
<tr>
<td>Paracentral</td>
<td>0.37±0.05</td>
<td>0.36±0.05</td>
<td>0.40±0.07</td>
<td>0.41±0.07‡</td>
<td>0.39±0.06</td>
</tr>
<tr>
<td>6A, %</td>
<td>Central</td>
<td>59.1±7.2</td>
<td>60.9±6.6</td>
<td>57.6±10.2</td>
<td>54.7±8.1‡</td>
</tr>
<tr>
<td>Paracentral</td>
<td>57.3±7.5</td>
<td>61.4±7.4</td>
<td>54.1±5.6</td>
<td>56.7±8.4</td>
<td>53.5±7.0</td>
</tr>
</tbody>
</table>

* Data are given as means±SD. PSX indicates pseudoexfoliation syndrome; ECD, endothelial cell density; CV, coefficient of variation of cell area; and 6A, percentage of hexagonal cells.
† P<.05, control group vs PSX group (Mann-Whitney U test).
‡ P<.001, changes from preoperative values; Wilcoxon signed rank test.
§ P<.05, control group vs PSX group (Mann-Whitney U test).
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was 2% (served in the PSX group. The total loss of hexagonality paracentral regions (Table 2).

Significant intergroup differences were observed in the central regions in the PSX group (Table 2). Hexagonal-progression increased gradually in the PSX group after 4 weeks, with more modest regional intergroup differences in the center after 6 months (Table 2).

On the first postoperative day, a rapid decrease in total endothelial hexagons by 5% (P=.006) was observed in the PSX group. The total loss of hexagonality was 2% (P=.62) in the control group. There were no significant intergroup differences. These transient changes were more pronounced in the center than in the paracentral regions in the PSX group (Table 2). Hexagonal-progression increased gradually in the PSX group after 4 weeks, with a total reduction from baseline of 3% after 6 months. Significant intergroup differences were observed in the paracentral regions (Table 2).

Table 3. Postoperative Endothelial Cell Loss After 6 Months*

<table>
<thead>
<tr>
<th>Region of Cornea</th>
<th>Control Group</th>
<th>PSX Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cells, No.</td>
<td>%</td>
</tr>
<tr>
<td>Central</td>
<td>−199±242</td>
<td>7.7±9.3</td>
</tr>
<tr>
<td>Paracentral</td>
<td>−366±361</td>
<td>12.4±11.5</td>
</tr>
<tr>
<td>Total</td>
<td>−282±266</td>
<td>10.3±9.5</td>
</tr>
</tbody>
</table>

* Data are given as mean±SD. PSX indicates pseudoexfoliation syndrome.
† Postoperative compared with preoperative values (Wilcoxon signed rank test).
‡ Changes from preoperative values: control group vs PSX group (Mann-Whitney U test).

study (Tables 1 and 2). Total polymegathism increased significantly in both groups postoperatively. The increase in cell size was more accentuated in the center in the control group (P=.007) and in the paracentral region in the PSX group (P=.002) (Table 2). This indicated a temporary heterogeneous cell size after surgery that then gradually returned to the baseline value during the postoperative period, with only modest regional intergroup differences in the center after 6 months (Table 2).

In the present study, patients with PSX had a significantly reduced preoperative ECD compared with age-matched controls. There was high concordance between both eyes in patients with PSX without previous surgery. Also, other studies reported a reduction of the central ECD ranging from 13% to 21%.1,2,4 In patients with PSX who were not operated on, Miyake et al.1 observed a decrease of hexagonality and an increased coefficient of variation. These observations suggest that the corneal endothelial changes represent a consistent finding in eyes affected with PSX. Based on clinical and electron microscopic evidence, a specific corneal endotheliopathy that may be more susceptible to the effects of surgery was postulated, which is distinguishable from other forms of corneal edema. It was clinically observed that in patients with PSX keratopathy, only moderate rises of intraocular pressure or minor intraoperative trauma might lead to a relatively early occurring diffuse corneal decompensation.5 Several primary and secondary pathogenetic causes for this corneal endotheliopathy were considered: (1) elevated intraocular pressure2,4,14; (2) hypoperfusion with relative ischemia affecting the anterior segment function5,16, (3) membrane destabilization caused by extracellular matrix deposition, particularly between the endothelial cells and the Descemet membrane, with focal desquamation due to loss of attachment to the endothelial layer and loss of polarity1; and (4) an iridopathy with impairment of the blood-aqueous barrier and development of aqueous humor abnormalities.1,10,17 A recent study could also demonstrate that PSX material is produced in situ by focally degenerating endothelial cells.3

Pseudoexfoliation syndrome is a systemic disorder that probably results from multifocal abnormal metabolic processes of unknown etiology leading to primary cell changes and is characterized by accumulation of fibrillar material containing basement membrane components in the anterior segment of the eye and other organ systems.8 It is a frequent clinical feature seen in patients with cataracts because the prevalence increases with age.10 In patients with PSX, insufficient mydriasis was determined to be the most significant risk factor for zonular breaks or rupture of the posterior lens capsule with consequent vitreous loss during extracapsular cataract extraction.1-3 In addition, the risk of endothelial decompensation from a more pronounced endothelial trauma was assumed after intraocular procedures.1,4 Because these studies also have suggested that the presence of PSX could have an effect on the viability of the endothelium, we undertook serial examinations of the corneal endothelial responses to cataract surgery under controlled clinical conditions.

In the present study, patients with PSX had a significantly reduced preoperative ECD compared with age-matched controls. There was high concordance between both eyes in patients with PSX without previous surgery. Also, other studies reported a reduction of the central ECD ranging from 13% to 21%.1,2,4 In
the PSX group, with modest differences after 6 months compared with the control group. Because pleomorphism is indicative of a compromised endothelium with a reduced functional reserve, these subtle changes might reveal an impaired regeneration.

We excluded other factors with possible reduction of the endothelial cell function to determine the effect of PSX on the corneal endothelium. Frequently, pathological conditions such as a cornea guttata or glaucoma can be detected in patients with PSX. The presence of a preoperative cornea guttata is considered to be a particular risk factor for a postoperative endothelial cell loss. The addition of several preoperative factors could result in an increased endothelial instability and a more severe response to the effects of the surgical procedure, with a higher rate of acute and continued chronic cell loss compared with healthy eyes that have not undergone surgery.

As some recent clinical studies have reported, postoperative inflammation and fibrinous reactions occur more frequently in patients with PSX after cataract extraction. It is also known that an asymptomatic low-grade chronic inflammation of the anterior eye segment due to impairment of the integrity of the blood-aqueous barrier may diminish endothelial function in the long term. This could lead to a progressive decline in ECD after intraocular surgery, as it was demonstrated that in humans cell transformation continues for many years after recovery of a wound area damaged during lens extraction. Thus, the corneas of eyes affected with PSX might have a higher incidence of late postoperative decompensation. Future investigations examining alterations of pump function by pachymetry or cell permeability by fluorophotometry will possibly provide more information concerning the corneal endothelial function in patients with PSX.

In conclusion, we demonstrated that in patients with PSX, despite preoperative reduced ECDs compared with controls, no increased endothelial cell loss and no clinically relevant differences in the endothelial repair mechanisms were found after uneventful cataract surgery with scleral tunnel incision, phacoemulsification, and intraocular lens implantation. However, the risk of anterior chamber manipulations in patients with PSX with posterior capsular rupture and anterior vitrectomy should be emphasized. This could cause increased acute mechanical alterations and endothelial trauma, reducing the number of cells and, at the same time, increasing the rate of cell loss to a level at which functional decompensation might ensue. Due to preoperative reduced endothelial cell counts and a decreased functional reserve, these circumstances require caution and precise, careful techniques during surgery in patients with PSX.