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Original Research Article

A Comparative Assessment of the Corneal Endothelial Morphology in Primary Open Angle Glaucoma and Pseudo-Exfoliative Glaucoma Patients

Ashutosh Kumar Anand[1], Arjun Choudhary[2]

[1]Senior Resident, Department of Ophthalmology, Anugrah Narayan Magadh Medical College & Hospital, Gaya, Bihar, India.
[2]Professor and HOD, Department of Ophthalmology, Anugrah Narayan Magadh Medical College & Hospital, Gaya, Bihar, India.

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Corresponding author: Dr. Ashutosh Kumar Anand
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Abstract

Aim: To compare the ECD in these eyes in comparison with normal eyes without glaucoma.

Material & Methods: This was a cross-sectional study carried out at a Department of Ophthalmology, Anugrah Narayan Magadh Medical College & Hospital, Gaya, Bihar, India over a period of one year. Consecutive patients who were more than 18 years of age and diagnosed with either POAG or PXFG for a minimum duration of 6 months and willing to provide informed consent were invited to participate in the study.

Results: On univariate analysis, advancing age, higher IOP, longer duration of glaucoma, and having POAG and PXFG were associated with lower endothelial cell count**.**

Conclusions: Eyes with POAG and PXFG have lower endothelial cell count compared to age-matched controls.

Key words: Cornea, endothelial cell density, glaucoma, primary open-angle glaucoma, pseudoexfoliation glaucoma

Introduction

The corneal endothelium is a vital structure that does not regenerate and hence its integrity is essential to maintain corneal clarity. The endothelial cell density (ECD) gradually diminishes with age, and there is good evidence to show that cell loss is accelerated following anterior segment surgeries such as phacoemulsification and trabeculectomy. Corneal endothelial cell loss has been shown to occur in different forms of glaucoma. Primary angle-closure glaucoma is known to be associated with accelerated endothelial cell loss, [1] especially after acute attacks [2] and following peripheral iridotomy. [3] However, the relationship between ECD and various forms of open-angle glaucoma is less well studied. Some authors have shown no influence of open-angle glaucoma on the ECD, [4] others have shown lower ECD in eyes with primary open-angle glaucoma (POAG) but not with normal-tension glaucoma (NTG),[5] while other report lower cell counts in NTG compared to POAG. [6]

The ocular pathologies resulting from the deposition of this material include secondary open angle glaucoma, disturbances of the pre-corneal tear film, zonular weakness and dehiscence resulting in phacodonesis, angle closure glaucoma and lens dislocation, capsular rupture and vitreous release during cataract surgery, poor pupillary dilation, blood-aqueous barrier dysfunction and corneal endothelial decompensation. [7]

There are many studies of corneal endothelial changes in PXS eyes reporting lower endothelial cell density, [8-9] high coefficient of variation in cell area, and a lower percentage of hexagonal cells. [3-4] There are, however, several studies reporting no significant changes in endothelial cell density, [10] the coefficient of variation in cell area, [4-5] or the percentage of hexagonal cells in PXS eyes. The changes in corneal endothelial morphology in PXS eyes have been controversial.

In view of scarce and contradicting literature on the influence of open-angle glaucoma on ECD, and lack of direct head-to-head studies comparing the ECD in eyes with POAG and PXFG, we conducted a cross sectional study to compare the ECD in these eyes in comparison with normal eyes without glaucoma and find factors predictive of the ECD in these eyes.

Material & Methods:

This was a comparative study carried out at a Department of Ophthalmology, Anugrah Narayan Magadh Medical College & Hospital, Gaya, Bihar, India. Over a period of one year. The study was approved by the institutional ethics committee and was performed in accordance with the Tenets of the Declaration of Helsinki. Informed consent was obtained from all the participants before enrollment. Consecutive patients who were more than 18 years of age and diagnosed with either POAG or PXFG for a minimum duration of 6 months and willing to provide informed consent were invited to participate in the study.

Patients without glaucoma who were visiting the outpatient department for other reasons were enrolled as controls. Exclusion criteria included those with any form of angle closure, other diseases associated with secondary glaucomas such as uveitis, trauma, etc., preexisting corneal disease, coexistent retinal diseases affecting vision, and those who had previous ocular surgeries including cataract surgery. For controls, any diagnosis other than refractive error and age-related cataract were excluded from the study.

At time of enrollment, patients' demographics, duration of glaucoma, and history of systemic illness including diabetes and hypertension were recorded. The type and frequency of antiglaucoma medications were recorded for those with glaucoma. The best-corrected visual acuity (BCVA) was tested by a trained optometrist followed by a comprehensive dilated ophthalmic examination. Slit-lamp findings such as the presence of corneal lesions and documentation of PXF material were noted. Those with nuclear sclerosis or nuclear opalescence Grade 2 or worse, presence of posterior sub capsular cataract or cortical cataract more than 4 clock hours were considered to have significant cataract.

Gonioscopy was performed using the four-mirror standard gonioscopy under dim illumination and findings for angle configuration and presence of PXF material in the angle structures were recorded. IOP was measured during the study visit using the Goldmann applanation tonometry.

Dilated fundus examination was carried out to document the cup-to-disc (CD) ratio, neuroretinal rim, and retinal nerve fiber layer loss. Endothelial cell parameters including the cell density

(ECD), coefficient of variation (CV), and proportion of hexagonal cells was measured using the Topcon SP-3000P noncontact specular microscope (Topcon, Japan). Endothelial cells were counted using manual variable-frame technique and by automated counting of cells by the software of the specular microscope. In this method, the area of interest was marked, and the software counted the cells and gave the parameters automatically. The counts were repeated three times by a grader masked to the glaucoma status of the patient, and a mean of the three counts was used for statistical analysis.

On the day of enrolment, prior to dilatation, all patients with glaucoma also underwent automated visual field testing with the Humphrey visual field analyzer (HFA 3) using the SITA 30-2 standard protocol. The mean deviation (MD) and pattern standard deviation were recorded following a reliable visual field test. Central corneal thickness was also measured using ultrasound method. The main outcome measure was difference in ECD, CV, and proportion of hexagonality of corneal endothelial cells between eyes with POAG, PXFG, and normal eyes.

The required sample size was calculated to be 40in each group. In patients with bilateral disease, the eye with more severe glaucoma based on MD was chosen for statistical analysis. All continuous variables were expressed as mean with standard deviation or median with interquartile range (IQR) and categorical variables were expressed as proportions (n, %). The BCVA was converted into logarithm of minimal angle of resolution (logMAR) for statistical analysis. Group differences across the three groups in the continuous variables were analyzed using the analysis of variance or the Kruskal-Wallis test. Differences across the POAG and PXF groups were assessed using the student t-test of the Wilcoxon rank-sum test for nonparametric variables. Group differences across categorical variables were analyzed using the Chi-square or Fischer's exact test. Factors predicting the endothelial cell count were analyzed using univariate and multivariable linear regression analysis and results were expressed as beta-coefficients with 95% confidence intervals (CI). Covariates were selected from those with $P < 0.1$ at the univariate stage, and those who were felt to be clinically relevant to the outcome. The best-fit model was arrived at using step-wise forward and backward regression. Regression diagnostics were run to find the influence of outliers and other leverage points. All data were entered into Microsoft and imported into STATA 12.1 i/c statistical software package (STATA Corp, Fort Worth, Texas, USA) for statistical analysis. $P < 0.05$ was considered statistically significant.

Results:

We enrolled 150 eyes of 150 participants in the study with 50 eyes each in the controls, POAG and PXFG groups. The mean age of the participants was 60.8 + 5.5 years (median = 60 years, IQR = 50–70 years, range = 50–70 years) and 72% were men.

Normal eyes also had better parameters related to the quality of the endothelial cell layer such as lower CV and higher proportion of hexagonal cells [Table 1]. On univariate analysis, advancing age, higher IOP, longer duration of glaucoma, and having POAG and PXFG were associated with lower endothelial cell count [Table 2]. On step-wise variable selection, age was the only covariate used to adjust the endothelial cell count. In multivariable linear regression analysis adjusted for age, eyes with POAG had an endothelial cell count of 185 cells/mm^2 lower than normal eyes (95% CI = 146–244 cells lower, $P < 0.001$). Similarly, eyes with PXFG had an endothelial cell count of 215 cells lower than normal eyes (95% CI = 137–263 cells lower, $P < 0.001$)

Table 1: Comparison of the demographics and clinical parameters across the three groups

Variables	**Controls (*n*=50)**	**POAG (*n*=50)**	**PXFG (*n*=50)**	***P***
Age	61.4±5.6	59.4±6.4	60.2±5.8	0.38
Gender (men), *n*	36	34	30	0.57
Right eye, *n*	25	25	30	0.63
Systemic: Diabetes mellitus, *n*	0	10	0	0.001
Hypertension, *n*	12	14	10	
Diabetes mellitus + hypertension, *n*	0	1	0	
Best-corrected visual acuity	0.17±0.10	0.20±0.11	0.13±0.15**	0.28
Spherical equivalent	−1.42±3.8	−1.28±1.2	−1.46±3.3	0.66
Lens (cataract), *n* Glaucoma parameters	31	28	34	0.82
Intraocular pressure	15.2±2.5	19.9±3.6	23.4±2.2**	<0.001
Central corneal thickness	522±22	536±24	530±30	0.56
Cup-disc ratio	0.3±0.07	0.69±0.15	0.60±0.13**	<0.001
Mean deviation	-	−13.6±10.3	−12.4±8.7	0.67
Pattern standard deviation	-	5.83±3.4	6.47±3.8	0.53
Number of antiglaucoma medications	-	2.48±1.6	2.71±1.8	0.73
Duration of glaucoma (months) Endothelial cell parameters	-	12.6±4.6	10.3±3.5**	0.001
Endothelial cell density	2271±162	2173±212	21537±153	<0.001
Co-efficient of variation	30.7±1.8	34.6±4.8	34.6±3.6	<0.001
Percentage of hexagonality	55.10±3.2	49.6±5.8	48.3±4.9	<0.001

Table 2: Univariate and multivariable analysis predicting the endothelial cell count

Variable	**Interval**	**Univariate analysis**		**Multivariable analysis β coeff**
		β coeff	**95 % CI**	
Age	1 year increment	−18.95	−21.63-−14.2	−21.53
Intraocular pressure	1 mmHg increment	−16.33	−20.83-−9.5	-
Central corneal thickness	1 μ increment	−1.56	−2.9--0.5	-
Mean deviation	1 dB decrement	3.99	−16-7.9	-
Duration	1 month increment	−9.85	−19-−1.6	-
Primary open-angle glaucoma	Versus normal	−161.66	−238-−84.7	−186.38
Pseudoexfoliative glaucoma	Versus normal	−184.72	−262-−113	−229.52

Discussion:

As endothelial cells are lost, the remaining cells must grow to compensate and during this process they lose their characteristic hexagonal shape and homogeneous size. The trend towards further reduction in ECD as patient's progress from PEX to PEXG is likely related to endothelial damage from both elevated IOP and increased PEX severity, as endothelial loss has also been shown in patients with POAG. [15] Sarowa et al found a statistically significant lower ECD in PEXG eyes compared to POAG eyes, suggesting that elevated IOP and PEX are likely independent factors damaging the endothelium via separate mechanisms. [16]

Wang et al, [17], reported that their findings (decrease in the endothelial cell density, similar to the coefficient of variation in the cell area, and the percentage of hexagonal cells) might be explained by the fact that mild intraocular disturbances developed slowly over a long period and resulted in a decrease in corneal endothelial cells and their enlargement without transformation of their hexagonal shape.

Shah et al [18] proved that patients with PXG had thinner corneas than people with PXS without glaucoma (530.7 versus 553.9 μm) recording a variance in statistical significance reaching a level of $p < 0.001$. Yagci et al [19] and Sobottka et al. also noticed that people with PXG had thinner corneas than the patients of the control group. de Juan-Marcos et al[20] observed that there were no significant differences. Similar results found by Aghaian and colleagues [21]and Bechmann and colleagues. [22]

In PXFG, precipitation of the PXF material on the endothelial surface is thought to be due to production of PXF by the endothelial cells themselves, thereby indicating that the cells have altered metabolic activity and are prone for damage irrespective of raised IOP. [13] The increased pressure due to trabecular outflow obstruction probably adds to the stress on the endothelial cells, and hence, the ECD is found to be consistently lower in eyes with PXFG compared to eyes with PXF without glaucoma. [23-26]

Conclusion:

Eyes with POAG and PXFG have lower endothelial cell count compared to age-matched controls. Future studies should report on changes in ECD over time in glaucomatous eyes and identify factors predictive of accelerated endothelial loss

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