Comparative Analysis of Corneal Parameters in Pseudoexfoliation Syndrome and Glaucoma

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ABSTRACT

Purpose: To evaluate corneal endothelial parameters using specular microscopy (SM) in patients with unilateral pseudoexfoliation syndrome (PES) by comparing pseudoexfoliative eyes, their unaffected fellow eyes, eyes with pseudoexfoliative glaucoma (PEG), and healthy control eyes.

Materials and Methods: This retrospective study included patients who underwent cataract surgery. The study analyzed 33 patients with unilateral pseudoexfoliation syndrome (PES), including eyes with pseudoexfoliation (Group 1) and their fellow eyes without pseudoexfoliation (Group 2). In addition, 75 eyes of 54 patients with pseudoexfoliative glaucoma (Group 3) and 72 eyes of 36 healthy individuals (Group 4) were included. All eyes underwent SM to assess central corneal thickness (CCT), endothelial cell density (ECD), coefficient of variation (CV), and hexagonality percentage (HEX).

Results: The mean ages were similar among the groups, with no significant differences ($p = 0.512$). Mean ECD values were 2494.6 ± 426.6, 2521.8 ± 455.8, 2322.0 ± 492.2, and 2556.1 ± 401.0 cells/mm² in Groups 1–4, respectively. PEG eyes had significantly lower ECD compared to controls, while no significant difference was observed between PES eyes and their fellow eyes. CV, HEX, and CCT did not differ significantly among groups. In the PEG group, retinal nerve fiber layer (RNFL) thickness showed a positive correlation with CCT, whereas visual field mean deviation (MD) demonstrated a negative correlation with CCT. No significant correlations were found between RNFL or MD and ECD, CV, or HEX.

Conclusion: ECD was significantly reduced in PEG eyes compared to controls, suggesting endothelial damage may be more associated with glaucoma than PES.

Keywords: Endothelial cell density, Pseudoexfoliation glaucoma, Pseudoexfoliation syndrome, Specular microscopy

INTRODUCTION

Pseudoexfoliation syndrome (PES) is a systemic disorder characterized by the progressive production and accumulation of abnormal extracellular fibrillar material in anterior segment structures of the eye, such as the lens capsule, iris, ciliary epithelium, zonules, trabecular meshwork, and corneal endothelial cells, due to altered extracellular matrix metabolism.[1]

The prevalence of PES varies between 10–20% in individuals over the age of 60 and can reach up to 40% in those over 80. The prevalence also differs based on racial and ethnic backgrounds. Secondary open-angle glaucoma, zonular weakness, phacodonesis, lens subluxation or luxa-

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tion, capsular rupture, and vitreous prolapse during cataract surgery, insufficient pupil dilation, blood–aqueous barrier dysfunction, and corneal endothelial decompensation are all associated complications of this material accumulation.[2]

The cornea is a transparent, multilayered structure crucial for light refraction and directly affects visual quality. The innermost layer consists of a single layer of non-regenerative endothelial cells. While endothelial cell density naturally decreases with age, it can also be damaged by surgery, infection, or trauma.[3] Both PES and pseudoexfoliation glaucoma (PEG) are believed to impact the morphology and density of these endothelial cells.

Specular microscopy (SM) is a key non-invasive imaging tool for assessing the corneal endothelium. In SM, the percentage of hexagonal cells (HEX) indicates pleomorphism, reflecting variations in cell shape, while the coefficient of variation (CV) represents polymegatism, indicating variability in cell size. Endothelial cell density (ECD) reflects the number of cells per mm², and central corneal thickness (CCT) provides information about corneal hydration and structural integrity.

Whether patients with PEG exhibit more pronounced corneal endothelial changes compared to those with PES, and whether these findings can be used in the clinical management of patients at risk of glaucomatous damage, remains unclear.

Although the effects of PES and PEG on corneal endothelial cells have been investigated in numerous studies, this study aimed to evaluate corneal endothelial parameters using SM in eyes with PES, their fellow eyes without PES, and eyes with PEG, and to compare the findings with those of a healthy control group. Furthermore, the relationship between glaucoma severity and SM parameters in PEG patients was evaluated.

MATERIALS AND METHODS:

A retrospective review of the records of patients who underwent cataract surgery at the Ophthalmology Clinic of Sakarya University Training and Research Hospital between January 2020 and December 2023 was conducted. The study was planned in accordance with the principles of the Declaration of Helsinki, and approval was obtained from the local ethics committee (E-43012747-050.04-513193-478).

Detailed ophthalmologic examination notes, including best-corrected visual acuity measurement, intraocular pressure (IOP) measurement with Goldmann applanation tonometry, slit-lamp biomicroscopy, gonioscopy, and fundus examination, were reviewed for all patients. PES was defined as the presence of pseudoexfoliative material at the pupillary margin, lens capsule, or both eyes. PEG was diagnosed based on findings of elevated IOP (>21 mmHg), glaucomatous cupping of the optic nerve head, and visual field defects.

Patients over 60 years of age and with good SM image quality were included in the study. Subjects who had prior intraocular surgery, those with corneal dystrophy or degeneration, those with keratoconus, those with a history of systemic diseases that could affect the corneal endothelium, such as systemic connective tissue diseases, and those with previous ocular trauma were excluded from the study.

Based on clinical examination and diagnoses, the study population was divided into four groups. Group 1 included the eyes with pseudoexfoliation (PE) of 33 patients with unilateral PES. Group 2 included the fellow eyes of the same patients, in which no clinically detectable pseudoexfoliative material was observed on detailed slit-lamp examination of the pupillary margin and anterior lens capsule after pharmacologic pupil dilation. These eyes were analyzed as a separate comparison group to evaluate possible subclinical changes and were not considered a healthy control group; Group 3 consisted of 75 eyes of 54 patients diagnosed with PEG; and Group 4 consisted of 72 eyes of 36 healthy individuals without PES, PEG, or any ocular disease other than cataract. All data were retrospectively obtained by reviewing SM records of patients evaluated for cataract surgery.

Non-contact SM (Topcon SP-3000P, Japan) measurements performed before cataract surgery were reviewed for all patients. Image quality was visually assessed, and only images with clearly visible endothelial cell borders were included. Endothelial cell counting was performed automatically using the device software, and to ensure reliable measurements, at least 50 contiguous cells per image were analyzed. ECD, defined as the number of cells per mm², was assessed. Cell size variability was quantified using the CV, and cell shape regularity was evaluated by the percentage of hexagonal cells. Additionally, CCT was measured in micrometers.

In addition, the mean retinal nerve fiber layer (RNFL) thickness measured by optical coherence tomography (OCT) and the mean deviation (MD) values in visual field analysis for patients with PEG in Group 3 were examined.

Statistical analyses were performed using SPSS version 21.0 for Windows (SPSS Inc., Chicago, IL). The normality of numerical variables was assessed using the Kolmogorov–Smirnov test. Comparisons between paired eyes (Group 1: eyes with PES and Group 2: fellow eyes without PE) were performed using the paired t-test for normally distributed data and the Wilcoxon signed-rank test for non-normally distributed data. Comparisons among independent groups (Group 1 vs. Groups 3 and 4, and Group 2 vs. Groups 3 and 4) were performed using one-way analysis of variance (ANOVA) for parametric data and the Kruskal–Wallis test for non-parametric data. When a significant difference was detected by ANOVA, Bonferroni correction was applied for post-hoc multiple comparisons. For non-parametric data, post-hoc pairwise comparisons were performed using the Mann–Whitney U test with Bonferroni adjustment. Correlation analyses were conducted using Pearson's correlation coefficient for normally distributed variables and Spearman's rank correlation coefficient for non-normally distributed variables. A p value of <0.05 was considered statistically significant.

RESULTS

A total of 156 eyes were included in the study. Of these, 33 were classified as Group 1 (eyes with PES), 33 as Group 2 (eyes of the same patients without PE), 75 as Group 3 (eyes with PEG), and 72 as Group 4 (control group).

The mean ages were 72.38 ± 6.05 years for Groups 1 and 2, 73.23 ± 5.70 years for Group 3, and 70.38 ± 6.14 years for the control group, with no statistically significant difference observed among the groups (p=0.867).

Mean ECD values were 2494.61 ± 426.63 cells/mm² in eyes with PES (Group 1), 2521.79 ± 455.76 cells/mm² in fellow eyes (Group 2), 2322.04 ± 492.24 cells/mm² in PEG eyes (Group 3), and 2556.13 ± 401.02 cells/mm² in control eyes (Group 4). ECD did not differ between PES eyes and their fellow eyes (p = 0.776). Overall, ECD differed significantly among the groups (Groups 1, 3, and 4: p = 0.012; Groups 2, 3, and 4: p = 0.013), mainly reflecting lower values in PEG eyes compared with controls. No other pairwise comparisons were statistically significant (Table 1).

There were no significant differences in mean CV, HEX, or CCT values among the groups, The mean CV values were 29.73 ± 6.20% in Group 1, 30.54 ± 7.31% in Group 2, 28.71 ± 8.20% in Group 3, and 30.74 ± 7.40% in Group 4. No significant difference was observed between PES eyes and their fellow eyes (p = 0.340) or in group comparisons (Groups 1, 3, and 4: p = 0.392; Groups 2, 3, and 4: p = 0.327). Mean HEX values were 67.91 ± 5.84% in Group 1, 66.77 ± 5.86% in Group 2, 66.67 ± 9.97% in Group 3, and 67.58 ± 7.31% in Group 4, with no significant differences between any groups (Groups 1 vs 2: p = 0.066; Groups 1, 3, and 4: p = 0.966; Groups 2, 3, and 4: p = 0.698) (Table 1).

CCT was similar across all groups. Mean CCT values were 556.45 ± 36.29 µm in Group 1, 553.56 ± 35.47 µm in Group 2, 541.16 ± 77.67 µm in Group 3, and 562.22 ± 27.64 µm in Group 4. No significant differences were observed between PES eyes and their fellow eyes (p = 0.095), nor in comparisons among multiple groups (Groups 1, 3, and 4: p = 0.087; Groups 2, 3, and 4: p = 0.083) (Table 1).

All patients in the PEG group were using antiglaucomatous medications, with a mean number of 2.46 ± 1.33 drugs. Among these patients, 48.0% were using alpha-agonists, 61.3% beta-blockers, 46.7% prostaglandin analogs, and 58.7% carbonic anhydrase inhibitors. Since many patients were using more than one class of antiglaucoma medication, independent statistical comparisons between drug groups were not appropriate. Correlation analysis showed no significant relationship between the total number of medications and ECD, CV, HEX, or CCT values (p=0.575, p=0.490, p=0.090, and p=0.718, respectively)(Table 2).

In patients with PEG, the RNFL thickness measured by OCT was 74.93 ± 17.39 µm, while the MD value measured by BGA was -8.96 ± 8.11. There was a significant correlation between RNFL and MD values and the total drug molecule used (p1=0.0001, r1=-0.669, p2=0.032, r2=0.468). In the correlation analyses performed between RNFL and MD values and ECD, AVG, CV, and HEX values, no sta-

Table 1: *Comparison of Demographic and Corneal Endothelial Parameters Among Study Groups*

	Group 1 (Eye with PES) n:33	Group 2 (Fellow eye without PE) n:33	Group 3 (PEG) n:75	Group 4 (Control) n:72	p1	p2	p3
Age (years)	72.38 ± 6.05	72.38 ± 6.05	73.23 ± 5.70	70.38 ± 6.14	-	0.867	0.867
ECD(cells/mm^2)	2494.61±426.63	2521.79±455.76	2322.04±492.24	2556.13±401.02	0.776	0.012*	0.013*
CV (%)	29.73±6.20	30.54±7.31	28.71±8.20	30.74±7.40	0.340	0.392	0.327
HEX (%)	67.91±5.84	66.77±5.86	66.67±9.97	67.58±7.31	0.066	0.966	0.698
CCT (µm)	556.45±36.29	553.56±35.47	541.16±77.67	562.22±27.64	0.095	0.087	0.083

ECD: Endothelial cell density, CV: Coefficient of variation, HEX: Hexagonality, CCT: Central corneal thickness, PES: Pseudoexfoliation syndrome, PE: Pseudoexfoliation, PEG: Pseudoexfoliation glaucoma

p1: Comparison between Group 1 (eyes with PES) and Group 2 (fellow eyes without PE) using the paired t-test or Wilcoxon signed-rank test.

p2: Comparison among Group 1 (eyes with PES), Group 3 (PEG), and Group 4 (control) using one-way ANOVA or the Kruskal–Wallis test.

p3: Comparison among Group 2 (fellow eyes without PE), Group 3 (PEG), and Group 4 (control) using one-way ANOVA or the Kruskal–Wallis test.

*For ECD, one-way ANOVA with Bonferroni correction and Kruskal–Wallis followed by Mann–Whitney U tests identified a significant difference only between Group 3 (PEG) and Group 4 (control) (p = 0.010 for p2; p = 0.012 for p3).

Table 2: *Correlation Analysis of RNFL Thickness, MD, and Number of Antiglaucomatous Medications with Corneal Endothelial Parameters in PEG Eyes*

	ECD (cells/mm²)	CV (%)	HEX (%)	CCT (µm)
RNFL thickness (µm)	r = -0.165	r = 0.143	r = -0.223	r = 0.367
	p = 0.261	p = 0.331	p = 0.056	p = 0.010
MD (dB)	r = -0.287	r = -0.064	r = 0.057	r = -0.530
	p = 0.164	p = 0.760	p = 0.788	p = 0.006
Number of medications	r = 0.103	r = 0.067	r = 0.378	r = 0.064
	p = 0.575	p = 0.490	p = 0.090	p = 0.718

RNFL: retinal nerve fiber layer; MD: mean deviation; ECD: endothelial cell density; CV: coefficient of variation; HEX: hexagonality; CCT: central corneal thickness.

Correlation analyses were performed using Pearson/Spearman correlation tests.

tistically significant correlation was observed ($p > 0.05$). A significant positive correlation was observed between RNFL thickness and CCT ($p = 0.010$, $r = 0.367$), while CCT showed a significant negative correlation with MD values ($p = 0.006$, $r = -0.530$), indicating that central corneal thickness decreased with increasing glaucoma severity (Table 2).

DISCUSSION

This study compared corneal SM data among eyes with unilateral PES, fellow eyes of the same patients, PEG eyes, and a healthy control group. The findings showed that ECD was statistically significantly lower in eyes in the PEG group compared to the control group. However, no significant difference in ECD was found between eyes with PES and fellow eyes of the same patients without PE, or between both groups and the control group.

Different findings have been reported in the literature regarding the effects of PES on the corneal endothelium. Bozkurt et al. reported that ECD was significantly reduced in PEG eyes compared to the control group, but this difference was not statistically significant in PES eyes without glaucoma.[1] These results are consistent with our study and support the notion that glaucoma is an important factor that accentuates the effect of PE on the corneal endothelium.

Some researchers, such as Knorr et al. and Schlötzer-Schrehardt et al., have demonstrated that PE can lead to structural and functional impairments not only in the trabecular meshwork but also in the corneal endothelium. These deteriorations include loss of endothelial cell morphology, decreased polygonality, intracellular inclusions, and retroendothelial deposits.[4,5] In our study, morphological parameters such as CV and HEX were evaluated in addition to ECD. However, no significant difference was found between the groups in terms of these morphological variables. This finding suggests that PE may not always significantly affect endothelial morphology or may have limited effects at the subclinical level.

In th e study by Inoue et al., ECD values were significantly reduced in patients with PES compared to the control group, but no significant difference was found in HEX and CV.[6] Similarly, Wang et al. reported a significant decrease in ECD; however, they noted no significant changes in morphological parameters such as HEX and CV.[7] In our study, although an absolute decrease in ECD was found between the eyes with PES and the control group, this difference was not statistically significant. This suggests that there may be subclinical endothelial damage in the early stages of PES.

The significantly lower corneal ECD observed in the PEG group suggests that PES, associated with glaucoma, may more significantly damage the corneal endothelium. PES has been shown to impair endothelial cell function through pathological mechanisms such as microfibrillar material accumulation in the anterior segment and increased local inflammatory activity. In addition, glaucoma-related factors such as prolonged intraocular pressure elevation and long-term use of topical antiglaucoma medications can further exacerbate endothelial cell loss.[5,8] Therefore, the reduced corneal ECD observed in eyes with PEG likely reflects the combined impact of pseudoexfoliation pathology and glaucoma-related factors, rather than a single causative mechanism.

The lack of a significant difference between eyes with PES and contralateral eyes without PE in our study supports the possibility that PES may have systemic or bilateral effects. This finding is consistent with studies indicating that PES, although often initially unilateral, can evolve into a bilateral process over time. Therefore, fellow eyes should not be regarded as truly healthy but rather as eyes that may represent an early or subclinical stage of pseudoexfoliation. Indeed, the lower ECD values in fellow eyes without PE compared to the control group, although not statistically significant, may indicate a subtle or early-stage impact. The control group's highest mean ECD was an expected result.

Because ECD may be lower in eyes with PEG, careful preoperative planning is necessary when intraocular surgery is considered in these patients. Reduced endothelial reserve can increase susceptibility to postoperative corneal complications, especially during cataract surgery. Therefore, preoperative endothelial assessment using SM can be clinically valuable, particularly in patients with PE and associated glaucoma.

In our study, although a significant correlation was observed between mean RNFL thickness and MD values and CCT in eyes with PEG, no significant relationship was found with other corneal endothelial parameters, including ECD, CV, or HEX. These findings suggest that CCT should be evaluated as an independent structural or biomechanical parameter in PEG.

The relatively large standard deviation of CCT values in the PEG group indicates inter-individual variability that may reflect biological heterogeneity or the presence of outliers. Furthermore, information on transient corneal edema, advanced glaucomatous changes, or drug-related corneal changes was not systematically collected; therefore, their potential impact on CCT measurements cannot be entirely ruled out.

Previous studies have highlighted the role of CCT as an independent risk factor for glaucoma development and progression. Specifically, CCT values below 555 µm have been shown to be associated with an increased risk of glaucoma and faster disease progression.[9] Consistent with these findings, the association observed in our study between thinner central corneal thickness and more advanced glaucoma may reflect increased susceptibility of ocular tissues to glaucomatous damage. Furthermore, thinner corneas may lead to lower intraocular pressure readings when measured by applanation tonometry, contributing to delayed diagnosis and treatment.

The European Glaucoma Prevention Study also identified CCT as an independent predictor of glaucoma development.[10] Moreover, Lee et al. demonstrated morphological differences in the lamina cribrosa between eyes with thin (<500 μm) and normal CCT; It was associated with thinner corneas, deeper lamina cribrosa placement, and greater posterior displacement.[11] These findings support the hypothesis that thin CCT may reflect the overall biomechanical fragility of ocular tissues, including the lamina cribrosa.

STUDY LIMITATIONS

This study has several limitations. First, the relatively small sample sizes in the subgroups may have limited the statistical power. Second, fellow eyes classified as clinically unaffected may still have subclinical pseudoexfoliation-related changes, given the bilateral and systemic nature of pseudoexfoliation syndrome. This potential subclinical involvement may have reduced the detectable differences between groups. Third, clinical parameters such as the duration of pseudoexfoliation, severity of the disease, duration of glaucoma, cumulative intraocular pressure exposure, and duration of antiglaucomatous treatment were not available for all patients; therefore, correlation analyses between these variables and ECD could not be performed. Additionally, the potential effects of long-term topical antiglaucomatous medications and chronic mechanical or oxidative stress on corneal endothelial health could not be fully evaluated. These limitations should be considered when interpreting the results of the present study.

CONCLUSION

The findings of this study suggest that PES alone has a limited effect on endothelial cell density, but this effect becomes more pronounced when glaucoma develops. Therefore, in patients diagnosed with PES, not only the optic nerve but also the corneal health should be closely monitored; endothelial assessment should be performed, particularly before surgical planning. This approach is important for reducing the risk of surgical complications and improving long-term visual outcomes.

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