Original Article

Corneal and anterior segment parameters in patients with clinically unilateral pseudoexfoliation syndrome

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ABSTRACT

Background: Pseudoexfoliation syndrome (PES) is an age-related systemic condition that predominantly affects ocular structures and is characterized by the deposition of material on the lens, ciliary body, zonules, corneal endothelium, iris, and pupillary margin. We compared the corneal endothelial morphology, anterior segment parameters, corneal densitometry, and corneal topographic characteristics between the clinically affected and apparently normal fellow eyes of patients with clinically unilateral PES.

Methods: This was a comparative, cross-sectional study of 34 patients with clinically unilateral PES. The anterior segment was examined using a Scheimpflug imaging system, and the corneal endothelium was assessed using a noncontact specular microscope. Corneal endothelial cell density, polymegathism, and pleomorphism were assessed using the specular microscope. Furthermore, the Scheimpflug camera was used to measure the corneal power of the flat and steep axis, mean corneal power, maximum keratometry, anterior chamber angle, anterior chamber depth, anterior chamber volume, corneal volume, and the corneal thickness at the apex point, center of the pupil, and the thinnest point. Corneal densitometry was evaluated at two concentric zones (0–2 mm and 0–12 mm).

Results: In total, 68 eyes from 34 patients were ultimately included in the study. The mean (standard deviation) age of the patients was 73.38 (8.75) years (range: 50–87 years). Among the included patients, 17 (50%) were male and 17 (50%) were female. The anterior segment parameters did not significantly differ between eyes with PES and their clinically unaffected fellow eyes (all $P > 0.05$). Similarly, no statistically significant difference was observed in corneal endothelial morphology (all $P > 0.05$).

Conclusions: Our measured parameters do not differ between the clinically affected eye and the clinically unaffected fellow eye. This supports the theory that PES is a bilateral disorder. Considering the variety of complications associated with PES, bilateral involvement should be assumed in the clinical and surgical management of patients with clinically unilateral PES. In the future, new research could increase our understanding of this syndrome.

KEYWORDS

exfoliation syndromes, glaucoma, exfoliation glaucoma, densitometry, light scattering, cornea, corneal topography, corneal endothelium, pseudoexfoliation syndrome

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INTRODUCTION

Pseudoexfoliation syndrome (PES) is an age-related systemic disease characterized by the abnormal production of extracellular granular material in intraocular and extraocular tissues. This material does not undergo degradation and progressively accumulates at its place of production [1]. It affects approximately 25% of the general population aged over 60 years, with its incidence increasing with age [2]. The prevalence depends substantially on ethnicity [3] and varies regionally within the same country. In Greece, the frequency of PES varies between 11.5% and 17% depending on the region [4].

The intraocular structures that produce the pseudoexfoliation (PEX) material include the lens capsule epithelium, nonpigmented ciliary epithelium, iris, vascular endothelium, trabecular endothelium, and basement membrane of the corneal epithelium and endothelium [5]. The deposition of PEX material in the anterior chamber may lead to a broad spectrum of ocular manifestations, such as increased intraocular pressure (IOP) with secondary open-angle glaucoma, cataract formation, phacodonesis due to zonular weakness, angle closure glaucoma due to lens dislocation, insufficient mydriasis, endothelial keratopathy, pre-corneal tear film disturbances, and blood-aqueous barrier dysfunction [6].

Patients with PES might also present systemic manifestations. These mainly include cerebrovascular and cardiovascular diseases, such as arterial hypertension, transient ischemic attack, myocardial infarction, stroke, abdominal aortic aneurysm, cerebral ischemia, thrombosis, embolism, hemorrhage, Alzheimer's disease, and sensorineural hearing loss [2, 7, 8].

Published studies have supported the theory that PES is usually a bilateral but asymmetric condition. Although roughly half of PES cases initially demonstrate only unilateral grayish fibrillar material in the anterior segment, which is observed by slit-lamp examination, over time, 74–81.6% of these cases convert to bilateral deposition of PEX material [9].

Moreover, using transmission electron microscopy, 81% of clinically unilateral PES cases have observable PEX material on the lens capsule or on the conjunctiva of the clinically unaffected eye [10]. Additionally, a study using transmission electron microscopy and immunochemistry that investigated clinically unilateral PES and their control eyes, suggested that PES is a bilateral but asymmetric disorder [11]. This asymmetry, which decreases with increasing age, may be due to subtle differences in ocular blood flow [12], blood-aqueous barrier function, aqueous humor dynamics, or anterior segment morphology [7].

Because PES is a risk factor for the development and progression of glaucoma, as well as for potential complications during cataract surgery, evaluating the anterior segment parameters in PES is crucial during the ophthalmic examination [4]. Slit-lamp biomicroscopy is a subjective method for assessing the anterior segment of the eye. However, more recent objective imaging technologies, such as endothelial specular microscopy, confocal microscopy, ultrasound biomicroscopy, Scheimpflug imaging, and optical coherence tomography, are noninvasive and provide quantitative and qualitative assessment of all the ocular structures [13, 14].

Our study compared the corneal endothelial morphology, anterior segment parameters, and corneal densitometry of the clinically affected and apparently normal fellow eyes of patients with clinically unilateral PES.

METHODS

The protocol of this comparative, cross-sectional study was approved by the hospital ethics committee (251 Hellenic Airforce General Hospital, Athens, Greece). All patients received verbal and written information about the study and provided written informed consent before the examination. Patients were recruited consecutively among those visiting the Ophthalmology Clinic of the Hellenic Airforce General Hospital for routine examinations between January 1, 2021 and September 30, 2021.

The study population comprised all consecutive patients with clinically unilateral PES. We defined PES as the presence of PEX material within either eye at the pupillary border, on the lens surface (as a central disk or peripheral granular zone), or both [15]. The fellow eyes, which had no apparent clinical evidence of PEX material, were categorized as having subclinical PES. We confirmed the presence or absence of PEX material after pupillary dilation. We included only systemically healthy individuals with no PEX material deposition in the fellow eye, a best-corrected visual acuity better than 0.8 on the decimal scale, IOP < 21 mmHg, and a normal optic nerve head under slit-lamp examination with a 78-D lens (Volk Optical Inc., OH, USA) to avoid any confounding factors from topical medications.

We excluded individuals with systemic diseases associated with endothelial morphological alterations, such as diabetes mellitus [16], gout [17], chronic kidney disease [18], cancer [19-23], rheumatoid arthritis, systemic lupus erythematosus [24], and sleep apnea syndrome [25, 26]. Patients with any history of ocular surgery, trauma, inflammation, ocular disease other than PES, contact lens use, dry eye syndrome, or other corneal pathologies were also excluded from the analysis.

All included individuals underwent a complete ophthalmic examination including best-corrected visual acuity measurement using a Snellen chart (Auto Chart Projector CP 670; NIDEK Co., Ltd., Gamagori, Japan), gonioscopy using a Goldmann three-mirror lens (Volk Optical), IOP measurement using a Goldmann applanation tonometer (Model AT 900 Type T; Haag-Streit, Koeniz, Switzerland), slit-lamp biomicroscopy (Haag-Streit Photo-Slit Lamp BX 900; Haag-Streit), and fundus examination under a slit lamp using a 78-D lens.

Corneal endothelium was examined using a noncontact specular microscope (CEM- 530; NIDEK Co., Ltd., Japan). This device acquires 16 automatic images of a 0.1-mm^2 central corneal endothelial surface area and displays them on a screen. Immediately after scanning, the images are automatically sorted based on their quality [27]. Based on the examiner's judgment, the most suitable image was selected for automated cell detection using the manufacturer's software. This process measures the central corneal thickness, corneal endothelial cell density (CED), coefficient of variation, and hexagonality (Hex) [28]. All examinations were performed by the same examiner (G.M.), who was blinded to the affected eye of each individual.

The anterior segment was assessed using a noncontact, noninvasive rotating Scheimpflug camera system (Pentacam HR; Oculus GmbH, Germany) [29]. Examinations were conducted under standard dim-light conditions, and the patients had no prior contact ocular examinations or pupil dilations. We performed three measurements for each eye, selecting the one with the best alignment and fixation for data analysis. During each measurement, 25 radial tomographs were acquired.

To assess corneal density, the corneal apex was automatically located and a 12-mm-diameter area around the apex was analyzed. The 12-mm-diameter area was divided into four concentric annular zones: 0–2 mm (central), 2–6 mm, 6–10 mm, and 10–12 mm. The cornea was also subdivided based on depth into three different layers: anterior (the superficial 120 μm), central (between the other two layers), and posterior (the innermost 60 μm) [30]. Only the 0–2-mm zone, corresponding to the endothelial parameters measured with the specular microscope, and the total diameter (0–12 mm) values for corneal densitometry of the posterior layer and total corneal thickness (CT) were considered for analysis. We expressed corneal densitometry values in standardized grayscale units, ranging from 0 to 100, where 0 indicates maximum transparency and 100 indicates complete opacity [30].

Other anterior segment parameters, calculated using three-dimensional anterior segment analysis modules, included corneal keratometry (K) values of the flattest (K1) and the steepest (K2) axes, the mean corneal power (Km), maximum K reading (Kmax), anterior chamber angle at 180° (ACA), anterior chamber depth (ACD), anterior chamber volume (ACV), corneal volume (CV), CT at the apex point (regarded as central CT [CCT]), CT at the center of the pupil, and CT at the thinnest point. All Scheimpflug camera examinations were performed by the same examiner (G.M.), who was blinded to the affected eye of each individual.

Data analysis was performed using STATA version 13 (Stata Statistical Software; Stata Corporation, College Station, TX, USA). Kolmogorov–Smirnov test was used to assess the normality of the data. Qualitative data are presented as numbers and percentages. Normally distributed continuous data were compared between eyes using *t*-test and are summarized as means and standard deviations (SDs). All reported *P*-values are two-sided and interpreted using a significance level of 5%.

RESULTS

In total, 68 eyes from 34 patients were ultimately included in the study. The mean (SD) age of the patients was 73.38 (8.75) years (range: 50–87 years). Among the included patients, 17 (50%) were male and 17 (50%) were female.

Table 1 summarizes variables measured by Pentacam HR and specular microcopy. CT in the pupil center, apex, and thinnest location, K1, K2, Km, Kmax, CV, ACV, ACD, ACA, and pupil diameter did not significantly differ between clinically affected eyes and normal fellow eyes (all $P > 0.05$). Furthermore, CED, coefficient of variation, and Hex in the eyes with clinically obvious PEX material were not significantly different from those in their fellow eyes (all $P > 0.05$) (Table 1).

Additionally, corneal densitometry values of the posterior layer and total CT in the 0–2 mm and 0–12 mm zones were comparable between the eyes with PEX material and their clinically normal fellow eyes (all $P > 0.05$) (Table 2).

Table 1. Anterior segment and corneal endothelial parameters of study participants

Variables	PEX eye (n = 34), Mean ± SD	Fellow eye (n = 34), Mean ± SD	*P*-value
ACD (mm)	3.1 ± 0.4	3.1 ± 0.4	0.69
ACV (mm³)	121.7 ± 5.3	124.8 ± 31.7	0.69
ACA (degree)	30.9 ± 6.1	30.1 ± 8.1	0.65
Corneal volume (mm³)	58.8 ± 3.8	58.3 ± 3.6	0.59
Pupil diameter (mm)	2.8 ± 1.1	3.0 ± 1.3	0.52
Front corneal power (D)			
K1	43.6 ± 1.7	43.8 ± 1.8	0.77
K2	44.4 ± 1.7	44.4 ± 1.7	0.91
Km	43.1 ± 5.2	43.0 ± 5.5	0.98
Kmax	45.3 ± 1.8	45.4 ± 1.8	0.96
Pachymetric measurements (μm)			
Central	544.9 ± 30.9	539.7 ± 28.3	0.48
Apex	546.2 ± 30.4	542.1 ± 28.6	0.58
Thinnest	540.2 ± 31.0	535.3 ± 27.8	0.51
CED (cells/mm²)	2406.8 ± 259.5	2395.8 ± 418.7	0.89
Hexagonical cells (%)	69.5 ± 5.3	67.7 ± 5.4	0.17
Coefficient of variation	29.4 ± 3.6	30.5 ± 5.3	0.34

Abbreviations: PEX, pseudoexfoliaton; n, number of eyes; SD, standard deviation; ACD, anterior chamber depth; mm, millimeters; ACV, anterior chamber volume; mm³, cubic millimeters; ACA, anterior chamber angle; D, diopter; K1, flattest keratometry; K2, steepest keratometry; Km, mean keratometry; Kmax, maximum keratometry; μm, micrometers; CED, endothelial cell density; cells/mm², cells per millimeters of squared; %, percentage. Note: Coefficient of variation calculated as the standard deviation of the mean cell area divided by the mean cell area and is a unitless.

Table 2. Corneal densitometry values of study participants

Variable	PEX eye (n = 34), Mean ± SD	Fellow eye (n = 34), Mean ± SD	*P*-value
Posterior 60 μm (GSU)			
0–2 mm	15.5 ± 2.8	15.1 ± 2.6	0.64
Total diameter (0–12 mm)	21.0 ± 4.0	20.6 ± 3.7	0.72
Total thickness (GSU)			
0–2 mm	20.4 ± 2.4	20.2 ± 2.4	0.79
Total diameter (0–12 mm)	28.7 ± 5.4	28.3 ± 5.9	0.80

Abbreviations: PEX, pseudoexfoliaton; SD, standard deviation; μm, micrometers; GSU, grayscale units; mm, millimeters.

DISCUSSION

In patients with clinically unilateral PES, we observed no differences between the clinically affected eye and the clinically unaffected fellow eye in either the anterior segment parameters or the corneal endothelial and corneal properties.

Our study assessed the corneal transparency and endothelial quality in patients with PES. PES has been associated with a corneal endotheliopathy that might be misdiagnosed as Fuchs endothelial dystrophy [31]. In PES-associated keratopathy, a decrease in the number of endothelial cells and changes in the morphology of corneal endothelium are observed along with phagocytized melanin and PEX material on the corneal endothelium. Initially, these changes do not affect corneal transparency; however, in advanced stages, they lead to endothelial decompensation and corneal damage [8]. Theories regarding the causes of this endotheliopathy include the penetration of PEX material into Descemet's membrane, leading to the disruption of hexagonal connections and signaling of the endothelial layer, thereby promoting apoptosis [8]. Other suggested theories involve hypoxia of the anterior chamber that induces antioxidant stress and reduces levels of ascorbic acid [7, 32], changes in cytokines/chemokines in the anterior chamber and cornea [6, 33], changes in the blood-aqueous barrier and vascular endothelial dysfunction [7, 34], and compression of endothelial cells due to elevated IOP [35]. Although we found comparable corneal characteristics between clinically affected and unaffected fellow eyes in patients with PES, further studies recruiting a normal control group may provide additional clinically relevant insights.

In studies evaluating the corneal endothelial changes in PES, CED has been observed as either decreased [36-39] or not significantly different [40] from that of the control group. Comparisons between eyes with PEX and their clinically unaffected fellow eyes, have reported either a lower CED or no significant difference [41]. In our study, CED in eyes with PEX was not significantly different from that of the clinically unaffected fellow eyes, similar to findings for both pleomorphism and polymegathism. These results support the theory that PES is a bilateral condition, with the PEX material appearing far earlier than the moment it is clinically observed on slit-lamp examination [10].

Although specular microscopy is used to assess the corneal endothelium, Pentacam HR calculates CV [30]. This can assess the whole cornea and could indicate the degree of endothelial damage. Relevant studies have shown no differences between patients with PES and controls [42, 43]. Consistent with these results, our study revealed no significant differences between eyes with PEX and their fellow eyes presenting no apparent clinical evidence of PEX material using both imaging systems.

Regarding corneal densitometry, our study revealed no significant difference in the total and posterior corneal density between eyes with PEX and their fellow clinically healthy eyes. Many studies have shown significantly increased density in the total cornea and in each separate corneal layer, in eyes with PEX and their fellow eyes when compared with that of controls [40, 44-46]. In accordance with our results, Sekeroglu et al. [47] found no statistical difference between eyes with PES and controls. Tear film abnormalities and corneal microstructural alterations might underlie an increase in corneal density. More specifically, tear osmolarity has been observed to be higher in both eyes of patients with unilateral PES compared to that of healthy eyes [48]. Electron microscopy of the corneal stroma in eyes with PEX has revealed accumulation of amorphous fibrous-granular material in the cytoplasm of metabolically active keratinocytes and in the surrounding extracellular space [8]. These alterations, coupled with the corneal endothelial irregularities associated with PES [39], could affect stromal hydration and contribute to the increased corneal density and decreased corneal transparency in eyes with PEX [46]. We did not measure tear film abnormalities, which could influence corneal density Therefore, further longitudinal studies incorporating additional clinical ocular characteristics could provide more information on the natural disease progression of PES and relevant outcomes for clinicians to properly manage this condition.

Accurate CT measurement is essential for the diagnosis of glaucoma prior to refractive and other ocular surgeries [49]. In this study, CT at the apex, the center of the pupil, and the thinnest point did not significantly differ between eyes with PEX and their fellow eyes. This is consistent with observations in many studies revealing no significant differences in CCT between eyes with PEX, their fellow eyes, and controls [9, 41-43, 46]. However, some authors have noted higher [49] or lower CCT [37, 50, 51] in eyes with PEX than that of healthy eyes. These contradictory CCT values in eyes with PEX could relate to different ethnicities, a variable numbers of study participants, or differences in measurement techniques.

Patients with PES appear to have a clinically rigid iris with reduced dilating ability [52, 53]. Reportedly, patients with pseudoexfoliation glaucoma (PEG) might have a smaller pupil. However, some studies have shown no statistically significant difference among PES, PEG, and control conditions [42]. Similarly, in our study, pupil diameter of eyes with PEX and their fellow, clinically unaffected eyes did not differ significantly.

Other anterior segment parameters such as ACD, ACA, and ACV are important in the diagnosis and evaluation of different types of glaucoma [54]. PEG is considered an open-angle glaucoma. However, proposed mechanisms of angle closure glaucoma in patients with PEX [55] include posterior synechiae, zonular weakness, enlargement of the lens due to cataract formation, and increased iris thickness predisposing to pupillary block [6]. A study showed that patients with unilateral PES have a more mobile lens in the affected eye and a shallower anterior chamber when the head is in prone position [44]. In other studies, while ACA did not differ significantly among eyes with PEX, the unaffected fellow eyes, and the controls, ACD and ACV in eyes with PEX were found to be similar or lower. However, in these studies, a lower ACD in the affected eyes was not accompanied by a lower ACV, and vice versa [32-35, 44]. In our study, these parameters did not differ significantly between eyes with PEX and their fellow, unaffected eyes. This pattern was also noted regarding the K values.

We observed comparable corneal topography and densitometry, corneal endothelium, and anterior chamber parameters in eyes with clinical PES and their apparently normal fellow eyes. Among the limitations that we encountered in our research, we emphasize the limited sample size, single-institution design, and non-randomized sampling. We did not employ a healthy control group to perform comparative studies and we did not measure tear film abnormalities, which could influence corneal density Therefore, further longitudinal studies incorporating a healthy control group and additional clinical ocular characteristics could provide more information on the natural disease progression of PES and relevant outcomes for clinicians to properly manage this condition.

CONCLUSIONS

We observed no differences in either the anterior segment parameters or the corneal endothelium and corneal properties between eyes with PEX and their clinically unaffected fellow eyes. This supports the hypothesis that PES is a systemic, bilateral, asymmetric disorder. Considering the variety of complications associated with PES, bilateral involvement should be assumed in the clinical and surgical management of patients with clinically unilateral PES. In the future, new research could increase our understanding of this syndrome.

ETHICAL DECLARATIONS

Ethical approval: This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the hospital ethics committee (251 Hellenic Airforce General Hospital, Athens, Greece). All patients received verbal and written information about the study and provided written informed consent before undergoing examinations.
Conflict of interest: None.

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