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Scheimpflug Camera Measurement of Optical Density of the Corneal Epithelium, Stroma, and Endothelium in Patients with Pseudoexfoliation Syndrome

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BDE 1 Dorota Urbaniak
CE 1,2 Małgorzata Seredyka-Burduk
BF 2 Waldemar Błoch
D 1,2 Grażyna Malukiewicz
AD 2,3 Bartłomiej J. Kałuzny

1 Department of Ophthalmology, Faculty of Medicine, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland
2 Department of Optometry, Faculty of Medicine, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland
3 Oftalmika Eye Hospital, Bydgoszcz, Poland

Corresponding Author: Małgorzata Seredyka-Burduk, e-mail: mburduk@wp.pl
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Background: The present study evaluated the optical density of particular layers of the cornea and anterior lens capsule in patients with pseudoexfoliation syndrome (PEX).

Material/Methods: Sixty patients with cataract and PEX (mean age 76.6±5.6 years, range 62–88 years) were compared to 55 controls with cataract without PEX syndrome (mean age 76.3±6.09 years, range 62–90 years; *P*>0.05). The anterior segment of one eye was examined in each patient using Pentacam HR by Oculus before the planned cataract surgery.

Results: The average optical density of the corneal epithelium, stroma, and endothelium was 25.3±6.09% and 19.9±3.41% (*P*<0.001), 23.1±5.5% and 19.2±3.6% (*P*<0.0001), and 14.6±3.4% and 12.3±2.1% (*P*<0.0001) in the PEX and control groups, respectively. The optical density of the anterior lens capsule was 13.6±4.2% in the PEX group and 9.74± 2.23% in the control group (*P*<0.0001). The average thickness of the cornea was 555 µm and 556 µm and the average optical density of endothelial cells 2240/mm^2 and 2323/mm^2 in the PEX and control groups, respectively (*P*<0.05).

Conclusions: In patients with PEX, increased optical density was observed not only in the structures with pseudoexfoliative material detectable by a slit-lamp), but also in the corneal epithelium and stroma. The increased optical density was not associated with reduced endothelial cell density or increased central cornea thickness.

MeSH Keywords: Corneal Pachymetry • Densitometry • Exfoliation Syndrome

Abbreviations: **PEX** – pseudoexfoliation syndrome; **LOCS** – nuclear color/opalescence parameter classification; **UBM** – ultrasound biomicroscopy

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Background

Pseudoexfoliation syndrome (PEX) is a disease associated with age that is characterized by the production and accumulation of extracellular matrix gray-white material in the anterior segment of the eye. This accumulation leads to basement membrane damage and the formation of degenerative cellular changes. Pathological material residue is also present in other organs, such as the skin, lungs, liver, cardiac muscle, kidneys, bladder, and cerebral meninges [1,2]. Only the ocular symptoms of PEX can be detected non-invasively. PEX is a frequent cause of secondary open-angle glaucoma, related to the deposition of pathological material in the trabeculum [3]. A significant issue from the clinical point of view is the increased risk of intraoperative complications during cataract surgery in patients with PEX [4]. The most common symptom of the disease is the deposition of exfoliative material at the anterior surface of the lens in the form of 3 zones of deposits in the front of the lens capsule, as observed by biomicroscopy in mydriasis [1,2]. In some patients with PEX, biomicroscopy can reveal deposits of exfoliative material adjacent to the corneal endothelium or incorporated into Descemet's membrane [5].

Exfoliative material is a complex of glycoproteins and proteoglycans that contain numerous cross-links. The material consists primarily of fibrillin-1, which forms the core of deposits and epitopes of elastic fibers, such as fibulin, emiline, vitronectin, amyloid P, tropoelastin, and elastin. Abnormal metabolism of the basement membrane results in the formation of exfoliative material components, such as laminin, nidogen, entactin, and fibronectin. Thus far, which compounds are the primary products of disturbed cellular metabolism and which have been re-built has not been resolved [6,7].

PEX symptoms, which can be observed during examination of the anterior segment within the pupil, are important for diagnosis but are relatively innocuous. More important is the presence of exfoliative material and its active production by the pre-equatorial region of the lens epithelium. Electron microscopy reveals visible fungoides aggregates of exfoliative material starting in the epithelium of the lens, elevating the surface of the capsule and separating the lens from the lens capsule. Similarly, within the unpigmented ciliary body region, the zonules separate from their connections to the basement membrane. Disintegration of the zonules can be intensified by the activity of lysosomal enzymes present in the exfoliative material, such as cathepsin B and metalloproteinases. These observations explain the detection of clinical zonular instability, increasing the risk of complications during cataract surgery [4].

Because PEX is a systemic disease and pathological material accumulates in many tissues, the translucency of the cornea may be reduced not only in endothelial cells, where substantial amounts of pseudoexfoliative material are observed, but also within the stroma or epithelium. As standard procedure, biomicroscopy is used to evaluate corneal transparency. This method is subjective, qualitative, and difficult to document. Imaging using a Scheimpflug camera allows for non-invasive and reproducible assessment of the morphometric parameters of the anterior segment and measurement of the optical density of the tissue. Previous studies have described optical density of the cornea in cases of keratitis, corneal dystrophy, and keratoconus, and to assess the status of the cornea following refractive surgery [8–10]. The optical density of the cornea in patients with PEX has received little research attention. Recently, Cankaya et al. confirmed that the presence of pseudoexfoliation material can decrease the transparency of the cornea [11]. However, Sekeroglu et al. reported contradictory results, as corneal clarity was similar in patients with bilateral PEX and healthy controls [12].

The aim of the present study was to evaluate the optical density of particular layers of the cornea and the anterior lens capsule in patients with PEX compared to a control group and to analyze the relationship between the optical density of the anterior lens and the optical density of individual layers of the cornea, corneal thickness, and the number of corneal endothelial cells.

Material and Methods

The study was carried out at the Department of Ophthalmology of Collegium Medicum, Nicolaus Copernicus University in Toruń, Poland. The research was approved by the Bioethics Committee of Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun (KB 141/2009). The study group consisted of patients admitted to the hospital for cataract surgery who were diagnosed with PEX during the pre-operative examination (PEX group). Typical exfoliative material on the anterior lens capsule during slit-lamp examination was observed. The control group consisted of patients hospitalized for cataract surgery but who did not have PEX. Additional inclusion criteria were age 50–90 years and intraocular pressure 10–21 mmHg. All patients consented to participate in the study. We excluded patients with myopia, significant subluxation of the lens, advanced changes in the endothelium, active uveitis or a history of uveitis, recent trauma, previous surgery on the examined eye, or unstable systemic diseases.

The PEX group consisted of 60 patients (40 women [66.7%] and 20 men [33.3%]) aged 62–88 years (average age 76.6±5.6 years). The control group consisted of 55 patients (35 women [63.6%] and 20 men [36.4%]) aged 62–90 years (average age 76.3±6.09 years). Age and sex did not significantly differ between the 2 groups. The hardness of the lens was evaluated in both groups using the LOCS classification (nuclear color/opalescence

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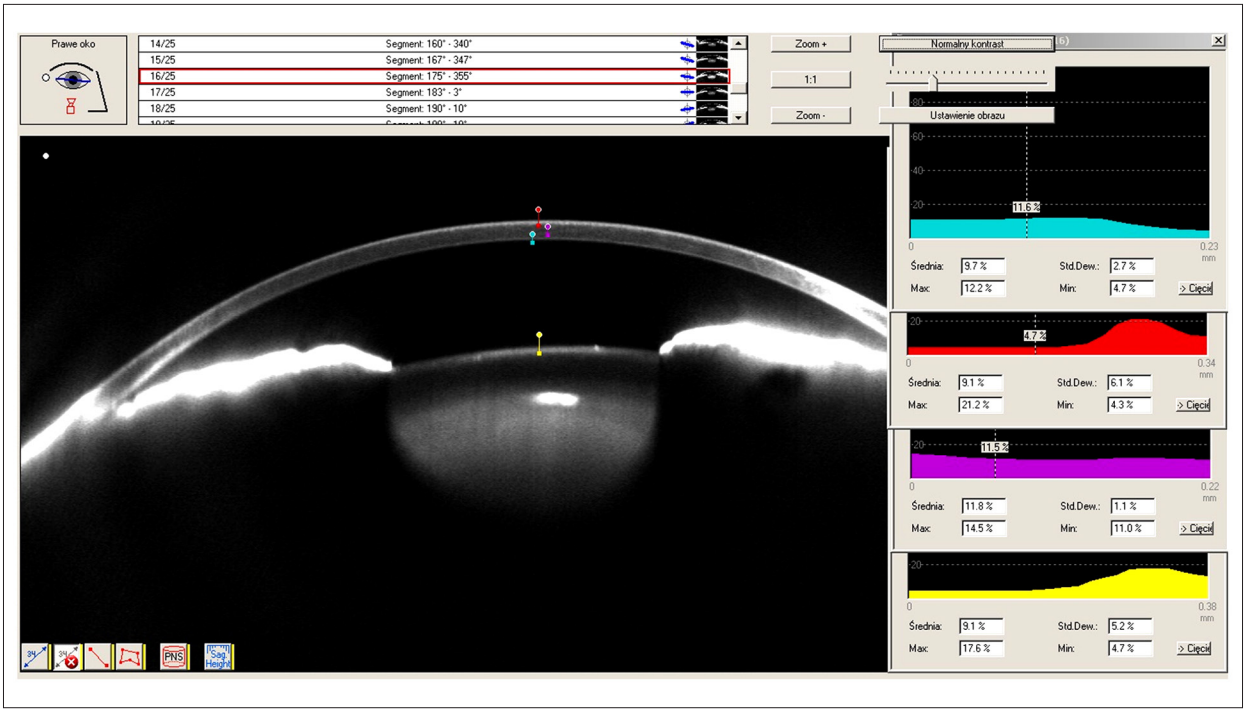

Figure 1. 0Scheimpflug camera measurement of the optical density of the epithelium, stroma, corneal endothelium, and anterior capsule of the lens.

parameter). The average hardness was 2.2±0.6 in the PEX group and 2.4±0.5 in the control group (P>0.05).

Each patient underwent a comprehensive examination of the eye scheduled for cataract surgery and assessment of the anterior segment using Pentacam HR (Oculus GmbH, Germany). The examination was carried out in a dark room in a sitting position, right after blinking, looking straight at the fixation point. Anesthetic or mydriatic drops were not administered. The same trained, blinded technician performed all measurements. During a single examination, 25 radial tomographs were made. Tomographs in the axis of 180±5°/0±5° were used for analysis. The optical density of selected elements of the anterior segment was measured by the same technician on the selected tomographs by drawing a line through the given structure in the automatically appointed visual axis. The camera analyzed the optical density of the selected structure, portrayed it as a graph, and provided numerical values for the minimum, average, and maximum optical density, expressed as the percentage of absorbed light. The analyses concerned the maximum optical density of the corneal epithelium, stroma, and endothelium, and the anterior lens capsule (Figure 1). The endothelial cell counts were measured with Topcon SP-3000P specular microscopy (Topcon Corporation, Tokyo, Japan). The examiner took a picture in the visual axis in the automatic mode and then the centers of at least 10 cells were manually marked in the alignment frame. Subsequently, the endothelial cells analysis was automatically performed by the instrument.

Statistical analyses used 2-fractions test, z-test, F-Snedecor test, and parametric tests to compare mean values. During the verification of hypotheses, a significance level of P=0.05 was established.

Results

Table 1 includes a comparison of the mean optical density of the corneal epithelium, stroma, and endothelium, as well as the anterior lens capsule in the PEX and control groups. For all parameters, the differences were highly significant.

The average thickness of the cornea was 555 µm in the PEX group and 556 µm in the control group. The average optical density of endothelial cells was 2240/mm^2 in the PEX group and 2323/mm^2 in the control group. No significant differences were found between the groups (Table 2) and the groups were homogenous with respect to these parameters.

The study also included an evaluation of the correlation between the optical density of the lens capsule (which can theoretically constitute a quantitative indicator of PEX severity), the age and sex of the patient, the thickness of the corneal epithelium, the optical density of the corneal stroma and endothelium, and the corneal endothelial cell count. Little positive correlation was found between the optical density of the anterior lens capsule and the age of the control group (Pearson

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Table 1. Optical density of the corneal epithelium, stroma, and endothelium and anterior lens capsule.

Group	Parameter	Epithelium (%)	Stroma (%)	Endothelium (%)	Lens capsule (%)
PEX	Number of eyes	60	60	60	60
	Min	17.3	11.4	9.8	7.1
	Max	42.7	39.2	23.9	23.1
	Mean	**25.3**	**23.1**	**14.6**	**13.6**
	SD	6.09	5.6	3.4	4.20
Control	Number of eyes	55	55	55	55
	Min	15.7	12.2	8.6	6.7
	Max	34.5	34.1	18.8	14.5
	Mean	**19.9**	**19.2**	**12.3**	**9.74**
	SD	3.41	3.6	2.1	2.23
	P	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**

Table 2. Evaluation of corneal thickness and corneal endothelial cell density.

Group	Parameter	Corneal thickness (µm)	Endothelial cell density (/mm²)
PEX	Number of eyes	60	60
	Min	480	755
	Max	655	3001
	Mean	**556**	**2240**
	SD	41	454
Control	Number of eyes	55	55
	Min	415	1289
	Max	665	3566
	Mean	**555**	**2323**
	SD	42	436
	P	**0.86**	**0.32**

correlation coefficient Rxy=0.326, *P*=0.02), and no such correlation was observed in the PEX group (*P*>0.05). In both groups, no correlation was found between the optical density of the anterior lens capsule and sex (*P*>0.05). A significant correlation was found between the optical density of the anterior lens capsule and the optical density of the corneal endothelial cells in only the PEX group. No correlations were found in regards to the other analyzed parameters (Table 3).

Discussion

The optical density analysis of the corneal epithelium revealed a significant difference between the groups, with a higher average optical density of the corneal epithelium in the PEX group than in the control group. Previous studies on PEX have reported an increased risk of postoperative edema of the corneal epithelium. Schlötzer-Schrehardt and Naumann reported an increased risk of inflammation and ulceration of the cornea due to chronic swelling in patients with PEX [13]. None of our patients had features of swelling of the corneal epithelium or inflammation. In addition, the endothelial cell density and pachymetry did not differ between groups. Therefore, the increased optical density of the corneal epithelium was not caused by swelling. Furthermore, during the course of PEX, even in patients with advanced keratopathy, stable histological changes do not occur in the corneal epithelium and Bowman's membrane, which could influence a change in the optical density. Only characteristics of edema of the corneal epithelium with a partial bullous separation of the epithelium

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Table 3. Correlation between the optical density of the anterior lens capsule and corneal thickness, the optical density of particular layers, and the number of corneal endothelial cells.

Parameter	PEX group			Control group		
	N of significant pairs	R_{xy}	*P*	N of significant pairs	R_{xy}	*P*
Corneal thickness	60	–0.177	0.18	55	–0.051	0.71
Optical density of the corneal epithelium	60	0.025	0.85	55	–0.154	0.26
Optical density of the corneal stroma	60	0.117	0.37	55	–0.030	0.83
Optical density of the corneal endothelium	60	**0.325**	**0.01**	55	0.048	0.73
Number of endothelial cells	60	–0.139	0.29	55	–0.049	0.72

from Bowman's membrane are observed [5]. Increased optical density of the corneal epithelium in PEX has not yet been reported in the literature. However, Cankaya et al. observed that the presence of pseudoexfoliation material decreased the transparency of the cornea as a whole [11].

Optical density analysis of the corneal stroma also revealed a significant difference between the groups, as the average optical density of the corneal stroma was higher in the PEX group than in the control group. Existing publications report increased optical density of the corneal stroma in the course of pathologies leading to the formation of clouding within the stroma. Otri et al. observed this dependence in patients with keratitis [8] and Elflein et al. in patients with mucopolysaccharidosis [9]. Electron microscopy of the corneal stroma in patients with PEX has revealed accumulation of amorphous fibrous-granular material in the cytoplasm of metabolically active keratinocytes and in the space surrounding these cells [6]. This will most likely affect the optical density of the corneal stroma, which may explain the increased optical density in our patients. Standard exfoliative material has not been reported within the corneal stroma.

The optical density of the corneal endothelium was significantly higher in the PEX group than in the control group. Schlötzer-Schrehardt et al. confirmed the presence of pseudoexfoliative material on the rear surface of the cornea [5]. This finding could be mistakenly interpreted as inflammatory deposits on the corneal endothelium [14]. Electron microscopy examination revealed a typical deposition of pseudoexfoliative material on the corneal endothelium and incorporation of the material into the posterior region of Descemet's membrane. In the affected areas of the corneal endothelium, irregularities and lack of continuity are observed, with loosely attached cells showing signs of degeneration, producing fibers of pseudoexfoliative material. These observations formed the basis of the theory of the incidence of PEX-specific keratopathy, which should be differentiated from typical Fuchs dystrophy [6]. In PEX-associated keratopathy, a decrease in the number and change in the morphology of corneal endothelium cells is observed, as well as the presence of large amounts of phagocytized melanin. In addition, diffused thickening of Descemet's membrane is observed on the striped layer, with the formation of irregular bulges and warts. In the initial stage of the disease, as in the population studied in our paper, this change does not affect corneal transparency. In advanced stages, a fibrous layer, loosely attached to Descemet's membrane, is formed [6,7]. The presence of these changes explains the increase in the optical density of the corneal endothelium. Although no reduction in the density of endothelial cells was observed in our patients with PEX, they may have had other characteristic features of the pathology within Descemet's membrane.

We also evaluated the optical density of the anterior lens at its central region. Theoretically, this parameter can be an exponent of PEX. The PEX group had a significantly higher optical density of the anterior capsule than in the control group. In previous studies, the anterior lens capsule was tested in eyes with PEX using ultrasound biomicroscopy, light microscopy, and electron microscopy. The common method of testing the signs of PEX is examination of the anterior surface of the lens under a biomicroscope. The basis for the diagnosis is pseudoexfoliative material deposits on the front of the lens capsule. Guo et al. confirmed the usefulness of ultrasound biomicroscopy (UBM) in examining the anterior lens capsule in PEX [15] by studying the thickness of the anterior lens capsule, as well as the presence of pseudoexfoliative material on the lens ligaments, in patients with clinical signs of PEX. Ruotsalainen et al. assessed the lens capsule using light microscopy. The lenses were obtained during cryoextraction of cataract in patients with and without PEX. The authors found no differences in the thickness of the anterior lens capsule between the 2 groups [16]. In an ultramicroscopy examination, Seland revealed fibers of exfoliative material with a thickness of 20–30 nm and length of 800–900 nm on the surface of the

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lens capsule, lens ligament apparatus, iris, ciliary body, trabeculum, conjunctival vessels, and tissues of the orbit [17]. Densitometry of the anterior lens capsule may potentially be useful in the objective assessment of PEX severity, but the amount of material in different zones is variable.

Krag et al. evaluated the effect of age on the biomechanical properties of the anterior lens capsule [18]. The thickness of the anterior capsule of the lens increases with age (~1.2%/year) until 75 years of age, and then it slightly decreases. In young people, the capsules are strong, durable, and highly extensible, whereas the anterior capsules of older donors are thicker, less elastic, and more brittle. These observations are somewhat in line with our results, which revealed a slight positive correlation between the optical density of the anterior lens capsule and the age of the patients in the control group, but no such correlation was found in the PEX group. In both groups, no correlation was found between the optical density of the anterior capsule and the sex of the patients.

The correlation between the optical density of the lens capsule and optical density of endothelial cells in the PEX group was probably caused by the deposition of pseudoexfoliative material on both the anterior capsule and the surface of the corneal endothelium, and this material is actively produced by corneal endothelial cells. No similar correlation was found between the optical density of the lens capsule and the thickness of the cornea, the number of endothelial cells, and the optical density of the epithelium and stroma. Scheimpflug camera examination may potentially be useful in the detection of a pseudoexfoliative material layer on the anterior surface of the lens in cases where observation by slit-lamp examination is impossible. The verification of the hypothesis of the possibility of using the Scheimpflug camera for early diagnosis of PEX in the subclinical stage seems to be an interesting topic for further research.

Conclusions

In summary, in patients with PEX, examination with a Scheimpflug camera revealed increased optical density not only in the structures in which the pseudoexfoliative material is visible (the front of the lens capsule and on the corneal endothelium), but also in the corneal epithelium and stroma. The increased optical density of the evaluated structures was not accompanied by a reduction in endothelial cell density or an increase in the thickness of the central cornea.

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