

## MORPHOLOGICAL FEATURES OF THE CORNEAL ENDOTHELIUM IN PATIENTS WITH PSEUDOEXFOLIATIVE GLAUCOMA

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✦ **Purpose.** To study the main morphological features of the corneal endothelium in patients with pseudoexfoliative glaucoma (PEG). **Methods.** We included 193 subjects aged from 55 to 75 years. The main study group (PEG) included 96 patients (192 eyes), the primary open angle glaucoma (POAG) group included 36 patients (72 eyes) with POAG, the PEX group included 31 patients (62 eyes) with pseudoexfoliation syndrome without glaucoma. The control group consisted of 30 healthy subjects (60 eyes). Main corneal endothelium parameters were evaluated using a non-contact endothelial microscope EM-935 (Haag Streit, Switzerland). Data were analyzed by STATISTICA 9 software for Windows. **Results.** The patients with PEG had lower endothelial cell density (ECD) in comparison to the control group ( $p < 0.01$ ), and PEX group ( $p < 0.05$ ). The polymegatism level in patients with PEG and POAG was higher than in the control group ( $p < 0.001$ , and  $p < 0.01$ , correspondingly). In patients with moderate and advanced PEG, the ECD was significantly lower ( $p < 0.01$ ), and the polymegatism level was significantly higher ( $p < 0.01$ ) than the same parameters in patients with early PEG. The lowest ECD and the highest polymegatism percentage were observed in PEG patients with more pronounced PEX manifestations,  $p < 0.05$ . No effect of IOP-lowering eye drops on the corneal endothelium parameters was revealed,  $p < 0.05$ . **Conclusions.** Significant morphological changes of the corneal endothelium (decreased endothelial cell density, increased polymegatism percentage) were revealed in patients with PEG. It was established that the severity of these changes is associated with the PEG and PEX severity. No effect of IOP-lowering eye drops on the corneal endothelium parameters was detected.

✦ **Keywords:** pseudoexfoliative glaucoma; pseudoexfoliation syndrome; endothelial microscopy.

## МОРФОЛОГИЧЕСКИЕ ОСОБЕННОСТИ ЭНДОТЕЛИЯ РОГОВИЦЫ У БОЛЬНЫХ ПСЕВДОЭКСФОЛИАТИВНОЙ ГЛАУКОМОЙ

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✦ **Цель.** Изучить морфологические особенности эндотелия роговицы у больных псевдоэксфолиативной глаукомой (ПЭГ). **Методы.** В исследование включено 193 человека в возрасте от 55 до 75 лет. Основную группу (ПЭГ) составили 96 больных (192 глаза), группу ПОУГ — 36 пациентов (72 глаза) с первичной открытоугольной глаукомой, группу ПЭС — 31 человек (62 глаза) с псевдоэксфолиативным синдромом без глаукомы. В группу контроля (ГК) вошли 30 человек (60 глаз), соответствующих критериям включения. Параметры эндотелия роговицы исследовали

при помощи бесконтактного эндотелиального микроскопа EM-935 (Haag Streit, Швейцария). Толщину центральной зоны роговицы (ЦЗР) измеряли ультразвуковым пахиметром AL-3000 (Tomey, Japan). Полученные в процессе исследования данные обрабатывали с использованием программной системы STATISTICA для Windows (версия 9). **Результаты.** У больных ПЭГ выявлена более низкая плотность эндотелия роговицы по сравнению с контролем ( $p < 0,01$ ) и ПЭС ( $p < 0,05$ ). Уровень полимегатизма при ПЭГ и ПОУГ был выше, чем в ГК ( $p < 0,001$  и  $p < 0,01$  соответственно). У больных ПЭГ с продвинутыми стадиями плотность эндотелия была достоверно ниже ( $p < 0,01$ ), а уровень полимегатизма оказался выше ( $p < 0,01$ ), чем при начальной стадии. Наименьшая ПЭ и наибольший процент полимегатизма наблюдались у больных ПЭГ с более выраженными проявлениями ПЭС ( $p < 0,05$ ). По сравнению с ГК наименьшая толщина ЦЗР выявлена у больных ПЭГ ( $p < 0,05$ ). Влияния гипотензивных глазных капель и их комбинаций на параметры морфологии эндотелия роговицы выявлено не было. **Выводы.** У больных ПЭГ имелись значительные морфологические изменения эндотелия роговицы (снижение плотности эндотелиальных клеток, повышение процента полимегатизма) и выраженность выявленных нарушений была ассоциирована с тяжестью ПЭГ и степенью выраженности ПЭС. Влияния гипотензивных глазных капель на параметры эндотелия роговицы обнаружено не было.

✧ **Ключевые слова:** псевдоэкзофолитивная глаукома; псевдоэкзофолитивный синдром; эндотелиальная микроскопия.

## INTRODUCTION

Pseudoexfoliation syndrome (PES) is an age-related generalized elastic microfibrilopathy (extracellular matrix pathology) characterized by chronic progressive accumulation of fibrillar material in the extraocular and intraocular tissues [1, 2].

Currently, the presence of PES is one of the main risk factors for pseudoexfoliative glaucoma (PEG) with both open and closed irido-corneal angle (ICA) [2, 3]. In addition to the eye, PES affects many other organs and tissues, in particular, skin, connective tissue elements of visceral organs, basal membranes of blood vessels, smooth and striated muscle tissue, and myocardium [4, 5]. There is evidence that PES may be associated with numerous extraocular diseases, including the pathology of the cardiovascular system, peripheral capillary disorders, vascular dysregulation, and neurodegenerative diseases, such as Alzheimer's disease [6–9].

The results of electronic microscopy showed that in the eye, pseudoexfoliative material (PEM) is capable of producing epithelial cells of the lens pre-equatorial zone, non-pigment epithelium of the ciliary body, pigment epithelium, almost all cell types of the iris stroma and vascular network, endothelium cells of the trabecular zone, and corneal endothelium. All of these conditions show signs of active fibrillogenesis [2].

Various studies have shown that PES affects most layers of the cornea, causing the development of a specific slowly progressive keratopathy and concomitant disturbances of the tear film and ocular surface [10–12]. Aspects of keratopathy in

PES are expressed through increased thickness of the Descemet's membrane of the PEM and result in its uneven thickening as well as in the capture of melanin by endothelial cells (ECs) [10]. In addition, a decrease in density and an increase in the level of polymegathism and polymorphism of the corneal endothelium were found in PES patients [11, 13, 14]. According to the results of several studies, patients with PEG have an even more pronounced degree of morphological changes in the endothelial layer of the cornea than patients with PES [13, 15, 16].

A few studies have shown that this group of patients is characterized by a decrease in the density of basal epithelium cells, anterior and posterior keratocytes, tortuosity and thinning of the nerve fibers of the subbasal nerve plexus, an increase in the number of dendritic cells, and the deposition of PEM in different layers of the cornea [11–13]. It has been surmised that the preceding changes may contribute to damage to the ocular surface, manifested as a decrease in the density of the superficial corneal epithelium, an increase in its desquamation, and the development of dry eye syndrome manifestations [11, 12, 17]. When assessing the thickness of the central zone of the cornea, PES patients and, to a greater extent, PEG patients had smaller values of this indicator compared with both the age-consistent control group and each other [18, 19].

The present work aimed to study the morphological aspects of the corneal endothelium in patients with PEG and to reveal their possible relationship with the manifestations of PES and glaucoma.

## MATERIAL AND METHODS

The study included 193 Caucasian patients (39% men, 61% women) aged from 55 to 75 years (mean age,  $66.5 \pm 0.4$  years) from St. Petersburg and the Leningrad Region of Russia.

All patients were divided into three groups and a control group. The PEG group consisted of 96 patients (192 eyes) with stage I–III PEG (38% men, 62% women), the primary open-angle glaucoma (POAG) group consisted of 36 patients (72 eyes) with stage I–III POAG (31% men, 69% women), and the PES group consisted of 31 patients (62 eyes) with pseudoexfoliation syndrome without glaucoma (42% of men, 58% of women). The control group included 30 patients (60 eyes) meeting the criteria for inclusion and exclusion (47% men, 53% women). The men-to-women ratio in the groups were similar. All patients signed a written informed consent to participate in the study.

The study did not include patients with a history of diabetes, cancer, and autoimmune diseases as well as severe concomitant pathology of various systems and organs. Referring to the eye, exclusion criteria comprised a history of uveitis, acute circulatory disorders in the central retinal artery and central retinal vein, injuries, corneal diseases, and wet age-related macular degeneration. In addition, contraindications to inclusion in the study were cataract surgery, glaucoma, a history of corneal pathology, and refractive surgery. The patients examined did not receive general or local therapy with glucocorticoids and immunosuppressants.

To confirm the diagnosis, all participants underwent a standard ophthalmologic examination, including autorefractometry, visometry, Maklakov tonometry, biomicrophthalmoscopy with undilated and dilated pupils, gonioscopy using Goldmann type lens (Olis, Russia), automated perimetry using the “fast threshold” strategy (AP-1000, Tomey Corp., Japan), and Heidelberg retinal tomography (HRT-II). The presence of pseudoexfoliative deposits was determined by biomicroscopy, biomicroscopy at medical mydriasis, and gonioscopy.

Evaluation of PES severity was performed according to the E.B. Eroshevskaya classification (1997), taking into account the severity of atrophy of the iris and number of pseudoexfoliative deposits [20]:

- *First degree* – mild atrophy of the iris, subtle exfoliative deposits on the anterior capsule of the lens and along the pupillary margin, pupil dilation up to 5 mm
- *Second degree* – pronounced exfoliation layering, atrophy of the pupillary pigment margin, redis-

tribution of the pigment on the iris and anterior chamber angle structures, pupil dilation up to 3.5–4.0 mm

- *Third degree* – significant atrophy of the iris and pigment border, deposits in the form of cellophane film, pronounced mixed pigmentation of all structures of the anterior chamber angle, phacodonesis, lack of pupil reaction to light

In addition, all patients underwent ultrasound keratopachymetry (AL-3000, Tomey Corp., Japan). The morphological state of the corneal endothelium was studied using an EM-935 contactless endothelial microscope (Haag-Streit AG, Köniz, Switzerland). The EM-935 is a portable device installed on a slit lamp (BQ 900, Haag-Streit AG, Köniz, Switzerland) that enables to analyze ECs in automatic and semi-automatic modes. Normal indices included EC density of more than 2000 cells/mm<sup>2</sup>, percentage of hexagonal cells of >60%, and polymegethism level of <30%.

The study was conducted at the Department of Ophthalmology and at the clinical and diagnostic center of the polyclinic, both of which are parts of the Pavlov First State Medical University of St. Petersburg.

The medical and biological data obtained during the study process were processed using STATISTICA 9.0 for Windows (TIBCO Software Inc., Palo Alto, CA, US). The frequency characteristics of the qualitative indices were analyzed using non-parametric methods  $\chi^2$ , Yates corrected  $\chi^2$  (for small groups), and Fisher criteria. Quantitative parameters in the studied groups were compared using the Mann–Whitney *U* test, Wald criteria, median  $\chi^2$ , and analysis of variance (ANOVA) module. Confidence intervals for frequency indices were calculated using the exact Fisher method. The characteristics of the samples were presented as mean  $\pm$  error of the mean ( $M \pm m$ ). To clarify the relationship between the studied parameters, a correlation analysis was performed and the Spearman correlation coefficient was calculated.

## STUDY RESULTS

The results of the quantitative assessment of the primary indices of the morphological state of the corneal endothelium and the central corneal thickness (CCT) in patients with PEG, POAG, and PES, and in the control group are presented in Table 1.

As seen in Table 1, the lowest density of corneal ECs was noted in patients with PEG compared to the control group and PES group ( $p < 0.01$  and  $p = 0.01$ , respectively). The ED indicator in the PEG group

compared to the POAG group and the ED indicator in the POAG and PES groups compared to the control group did not have significant differences ( $p > 0.05$ ). The percentage of hexagonal cells was not significantly different in the groups under study ( $p > 0.05$ ).

The most severe polymegathism was detected in patients with PEG and POAG compared to the control group ( $p < 0.001$  and  $p < 0.01$ , respectively). In addition, the level of polymegathism in PEG patients was significantly higher than in PES patients without glaucoma ( $p < 0.05$ ).

PEG patients had the lowest CCT compared with the control group ( $p < 0.05$ ). However, the CCT in PEG patients did not differ from the same parameter in the POAG and PES groups. It should be noted that CCT values in the POAG and PES groups were comparable with those of the control group.

In patients with PEG and POAG, the state of the corneal endothelium and the CCT value were evaluated depending on the stage of the glaucomatous process, whereas patients with developed and advanced stages of glaucoma were combined into one group (Table 2).

Table 1 / Таблица 1

**Endothelial cell density, percentage of hexagonal cells, and polymegathism, central corneal thickness in patients with pseudoexfoliative glaucoma, primary open angle glaucoma, pseudoexfoliation syndrome, and in the control group**

**Плотность эндотелиальных клеток, процент гексагональных клеток и полимегатизма, толщина центральной зоны роговицы у больных псевдозксфолиативной глаукомой, первичной открытоугольной глаукомой, псевдозксфолиативным синдромом и группы контроля**

Parameters	Control Group	PEG	POAG	PES	$p$
Endothelial cells density, cells/mm <sup>2</sup>	2660.9 ± 50.6	2498.5 ± 29.8	2556.1 ± 38.4	2643.9 ± 41.8	$p_1 < 0.01$ $p_2 = 0.05$ $p_3 = 0.01$
Hexagonal cells, %	48.4 ± 1.3	44.9 ± 0.8	47.3 ± 1.2	47.4 ± 1.3	$p > 0.05$
Polymegethism, %	46.5 ± 2.7	59.67 ± 1.7	56.9 ± 2.6	53.3 ± 2.5	$p_1 < 0.001$ $p_2 < 0.01$ $p_3 < 0.05$
CCT, $\mu\text{m}$	555.7 ± 4.1	546.3 ± 2.6	549.6 ± 5.0	553.0 ± 3.6	$p_1 > 0.05$

Note. CCT, central corneal thickness; PEG, pseudoexfoliative glaucoma; PES, pseudoexfoliation syndrome; POAG, primary open-angle glaucoma;  $p_1$ , comparison of indices between PEG and the control group,  $p_2$ , comparison of indices between POAG and the control group,  $p_3$ , comparison of indices between PES and PEG.

Table 2 / Таблица 2

**Endothelial cell density, percentage of hexagonal cells, and polymegathism, central corneal thickness in patients with mild and advanced stages of pseudoexfoliative glaucoma and primary open angle glaucoma**

**Плотность эндотелиальных клеток, процент гексагональных клеток и полимегатизма, толщина центральной зоны роговицы у больных с начальной (I) и продвинутыми (II + III) стадиями псевдозксфолиативной глаукомы и первичной открытоугольной глаукомы**

Indicators ( $M \pm m$ )	PEG I $n = 130$	PEG II + III $n = 55$	POAG I $n = 47$	POAG II + III $n = 22$	$p$
Number of endothelial cells, cells/mm <sup>2</sup>	2568.7 ± 30.7	2340.1 ± 66.3	2588.4 ± 45.9	2508.9 ± 77.3	$p_1 = 0.001$
Hexagonal cells, %	44.93 ± 1.07	45.4 ± 1.3	48.2 ± 1.5	44.5 ± 1.9	$p > 0.05$
Polymegethism, %	56.3 ± 2.0	66.8 ± 3.0	54.5 ± 3.1	61.1 ± 5.4	$p_1 < 0.01$
CCT, $\mu\text{m}$	550.6 ± 3.1	537.8 ± 4.7	556.5 ± 5.6	541.1 ± 10.6	$p_1 < 0.05$

Note. CCT, central corneal thickness; PEG, pseudoexfoliative glaucoma; POAG, primary open-angle glaucoma;  $n$ , number of eyes;  $p_1$ , comparison of indices between PEG I and PEG II + III.

As seen in Table 2, in patients with developed PEG, the density of ECs was significantly lower than that in patients with initial stage PEG ( $p = 0.001$ ). Further, high levels of polymegathism ( $p < 0.01$ ) and lower CCT ( $p < 0.05$ ) were typical to patients with severe PEG.

In patients with different POAG stages, there were no significant differences between the corneal endothelium indices ( $p > 0.05$ ). Also, the differences in the indices listed in Table 2 were not established when comparing patients with different stages of PEG and POAG ( $p > 0.05$ ).

The morphological state of the corneal endothelium and CCT were also evaluated in patients with

different PES severity in the PES and PEG groups (Table 3). As seen in Table 3, the lowest density of ECs and the highest level of polymegathism were observed in PEG patients with pronounced manifestations of PES ( $p < 0.05$ ). In addition, the EC density in PEG patients with more severe manifestations of PES was lower than in PES patients of the same severity ( $p < 0.05$ ).

Figure 1 shows the result of non-contact endothelial microscopy (EM 935, Haag-Streit AG, Köniz, Switzerland) and a photography of the anterior segment of the left eye of a 72-year-old patient with stage IIa PEG.

Table 3 / Таблица 3

**Endothelial cell density, percentage of hexagonal cells, and polymegathism, central corneal thickness in patients with different stages of pseudoexfoliation syndrome (pseudoexfoliation syndrome and pseudoexfoliative glaucoma)**

**Плотность эндотелиальных клеток, процент гексагональных клеток и полимегатизма, толщина центральной зоны роговицы у пациентов с различной степенью выраженности псевдозксфолиативного синдрома (псевдозксфолиативный синдром и псевдозксфолиативная глаукома)**

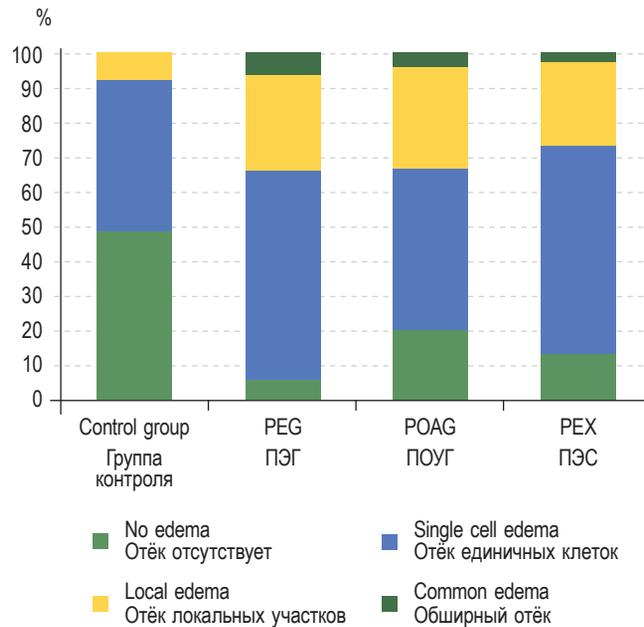
Indicators ( $M \pm m$ )	PEG1 ( $n = 94$ )	PEG2 ( $n = 95$ )	PES1 ( $n = 36$ )	PES2 ( $n = 26$ )	$p$
Number of endothelial cells, cells/mm <sup>2</sup>	2575.4 $\pm$ 38.2	2422.5 $\pm$ 44.4	2654.7 $\pm$ 63.6	2628.8 $\pm$ 48.2	$p_1 < 0.05$ $p_2 < 0.05$
Hexagonal cells, %	45.1 $\pm$ 0.9	44.8 $\pm$ 1.0	47.3 $\pm$ 1.9	47.5 $\pm$ 1.8	$p > 0.05$
Polymegathism, %	55.2 $\pm$ 2.4	64.0 $\pm$ 2.4	51.5 $\pm$ 3.5	55.9 $\pm$ 3.3	$p_1 = 0.01$
CCT, $\mu\text{m}$	547.1 $\pm$ 3.6	545.6 $\pm$ 3.7	551.0 $\pm$ 4.4	555.8 $\pm$ 6.5	$p > 0.05$

Note. CCT, central corneal thickness; PEG, pseudoexfoliative glaucoma; PEG1 and PES1, groups of patients with mild PES; PEG2 and PES2, groups of patients with moderate and severe PES manifestations; PES, pseudoexfoliation syndrome; n, number of eyes;  $p_1$ , comparison of indices between the PEG1 and PEG2 groups;  $p_2$ , comparison of indices between PEG2 and PES2 groups.



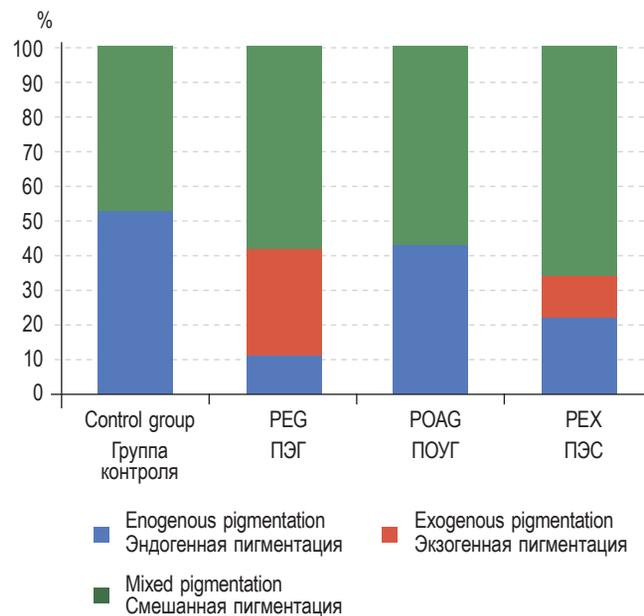
**Fig. 1.** Pseudoexfoliation material on the anterior segment structures (a); results of non-contact endothelial microscopy (EM-935, Haag Streit) in 72 years old female patient diagnosed with moderate pseudoexfoliative glaucoma (b)

**Рис. 1.** Псевдоэксфолиативные отложения на структурах переднего сегмента глаза (a); результаты бесконтактной эндотелиальной микроскопии (EM-935, Haag Streit) у пациентки 72 лет. Диагноз: о/у II «а» псевдоэксфолиативная глаукома (b)



**Fig. 2.** Corneal endothelial edema intensity in patients with pseudoexfoliative glaucoma, primary open angle glaucoma, pseudoexfoliation syndrome, and in the control group

**Рис. 2.** Степень выраженности отёка эндотелия роговицы у пациентов с псевдоэкзофоллиативной глаукомой, первичной открытоугольной глаукомой, псевдоэкзофоллиативным синдромом и группы контроля



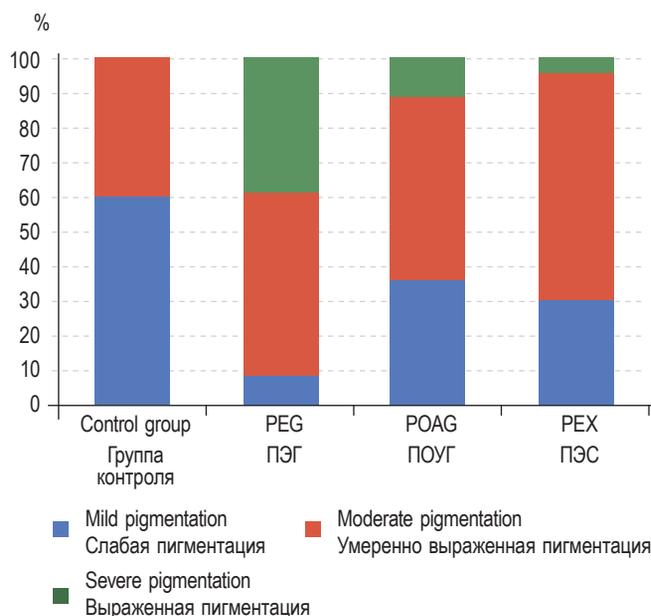
**Fig. 3.** Type of the iridocorneal angle pigmentation in patients with pseudoexfoliative glaucoma, primary open angle glaucoma, pseudoexfoliation syndrome, and in the control group

**Рис. 3.** Характер пигментации радужно-роговичного угла у пациентов с псевдоэкзофоллиативной глаукомой, первичной открытоугольной глаукомой, псевдоэкзофоллиативным синдромом и группы контроля

In all patients, the severity of corneal endothelial edema was assessed. Subclinical edema, detected only by endothelial microscopy, was noted in the overwhelming majority of cases. The edema was graded according to the following criteria: 0 – no edema of the endothelium, 1 – edema of individual ECs, 2 – edema

of some sections of the endothelium, and 3 – edema of large areas of the endothelium (subtotal edema).

Unlike the patients in the PEG, POAG, and PES groups, those in the control group either did not have edema at all or had a very mild edema of the corneal endothelium. Thus, in patients with PEG, POAG,



**Fig. 4.** Pigmentation intensity of the iridocorneal angle in patients with pseudoexfoliative glaucoma, primary open angle glaucoma, pseudoexfoliation syndrome

**Рис. 4.** Интенсивность пигментации радужно-роговичного угла у пациентов с псевдоэксфолиативной глаукомой, первичной открытоугольной глаукомой, псевдоэксфолиативным синдромом

Table 4 / Таблица 4

**Severity of iris dystrophy in patients with pseudoexfoliative glaucoma, primary open angle glaucoma, pseudoexfoliation syndrome, and in the control group**

**Выраженность дистрофических изменений радужной оболочки у пациентов с псевдоэксфолиативной глаукомой, первичной открытоугольной глаукомой, псевдоэксфолиативным синдромом и группы контроля**

Expression of Dystrophic Iris Changes	Control	PEG	POAG	PES	<i>p</i>
None, %	81.7	6.2	27.8	19.4	< 0.01
Mild, %	15.0	49.0	36.1	54.8	
Severe, %	3.3	44.8	36.1	25.8	

Note. PEG, pseudoexfoliative glaucoma; PES, pseudoexfoliation syndrome; POAG, primary open-angle glaucoma.

and PES, eyes with a more pronounced level of edema ( $p < 0.01$ ) prevailed (Fig. 2).

In addition to studying the state of the corneal endothelium, the nature and intensity of ICA pigmentation was evaluated in all patients included in the present study. Results indicated that in patients with PEG and PES, mixed and exogenous pigmentation of ICA was more common than endogenous pigmentation ( $p < 0.01$ ) (Fig. 3).

At the same time, in the PEG, POAG, and PES groups, a more pronounced intensity of ICA pigmentation was more typical compared to the control group, whereas in PEG patients, the number of eyes with the maximum degree of pigmentation was significantly higher ( $p < 0.01$ ) (Fig. 4).

Currently, there is no single classification of dystrophic changes of the iris in glaucoma [20, 21]. In the present study, in assessing the state of the iris, the severity of changes in the mesodermal layer, destruction and atrophy of the pupil margin, and level of pigment dispersion were taken into account. The disorders were classified according to the criteria proposed by N.A. Puchkovskaya et al. (1982) [22]. Changes corresponding to stages I and II of the process were joined in a group of mild changes, whereas those corresponding to stages III and IV were joined in a group of severe changes.

Table 4 shows that PEG patients had most severe dystrophic changes in the iris ( $p < 0.01$ ). In

Table 5 / Таблица 5

**Local IOP-lowering medications and corneal endothelium parameters in patients with pseudoexfoliative glaucoma and primary open angle glaucoma****Местные гипотензивные препараты и показатели состояния эндотелия роговицы у пациентов с псевдоэксфолиативной глаукомой и первичной открытоугольной глаукомой**

IOP-lowering Eye Drops and Their Combinations	PEG	POAG	<i>p</i> Cell Density (cells/mm <sup>2</sup> )	<i>p</i> Hexagonal Cells, %	<i>p</i> Polymegethism, %
	Number of Patients (%)				
PGL	25.0	31.9	> 0.05	> 0.05	> 0.05
β-Blockers	3.6	5.6			
α <sub>2</sub> -Adrenoceptor agonists	3.6	2.8			
CAI	4.7	0			
β-bl. + PGL	16.1	15.3			
β-bl. + α <sub>2</sub>	0.5	0			
PGL + CAI	14.6	8.3			
PGL + α <sub>2</sub>	1.6	2.8			
β-bl. + CAI	2.1	8.3			
PGL + β-bl. + CAI	14.6	12.5			
β-bl. + α <sub>2</sub> + PGL	0.5	0			
PGL + α <sub>2</sub> + CAI	1.6	1.4			
PGL + β-bl. + CAI + α <sub>2</sub>	3.1	0			
No drugs	7.8	6.9			

Note. α<sub>2</sub>, alpha-2-adrenoceptor agonists; β-bl., beta-blockers; CAI, carbonic anhydrase inhibitors; PEG, pseudoexfoliative glaucoma; PGL, prostaglandin analogs; POAG, primary open-angle glaucoma.

the same group, the number of eyes with normal structure of the iris was minimal ( $p < 0.01$ ). Significant changes were also observed in the POAG and PES groups; however, the severity of changes in these two groups was lower than that in PEG patients ( $p < 0.01$ ).

In patients with PEG and POAG, the possible effect of IOP-lowering eye drops and their combinations on the state of the corneal endothelium was assessed (Table 5). The results of the analysis showed that local IOP-lowering therapy had little effect on the condition of the corneal endothelium in either group ( $p > 0.05$ ).

Table 6 / Таблица 6

**Spearman correlation analysis results in patients with pseudoexfoliative glaucoma, primary open angle glaucoma, pseudoexfoliation syndrome, and in the control group****Результаты корреляционного анализа по Spearman у пациентов с псевдоэксфолиативной глаукомой, первичной открытоугольной глаукомой, псевдоэксфолиативным синдромом и группы контроля**

Parameters	Control group		PEG		POAG		PES	
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	R	<i>p</i>
EC density (cells/mm <sup>2</sup> ) – hexagonal cells (%)	–	–	0.16	< 0.05	–	–	0.29	< 0.05
EC density (cells/mm <sup>2</sup> ) – polymegethism (%)	–0.85	< 0.01	–0.87	< 0.01	–0.86	< 0.01	–0.73	< 0.01
Hexagonal cells (%) – polymegethism (%)	–	–	–	–	–	–	–0.37	< 0.01
EC density (cells/mm <sup>2</sup> ) – CCT (μm)	–	–	0.26	< 0.01	–	–	–	–
Polymegethism (%) – CCT (μm)	–	–	–0.28	< 0.01	–	–	–	–

Note. CCT, central corneal thickness (μm); EC density – corneal endothelial cell density (cells/mm<sup>2</sup>); PEG, pseudoexfoliative glaucoma; PES, pseudoexfoliation syndrome; POAG, primary open-angle glaucoma.

When conducting a correlation analysis in all groups under study, a strong negative correlation was found between the density of ECs and the level of polymegethism ( $p < 0.01$ ) (Table 6). In addition, in patients with PEG and PES, a weak positive correlation was found between pigment epithelial cells and percentage of hexagonal cells ( $r = 0.16$ ,  $p < 0.05$  and  $r = 0.29$ ,  $p < 0.05$ , respectively). In the group of PEG patients, a negative correlation was established between the CCT and the level of polymegethism ( $r = -0.28$ ,  $p < 0.01$ ), and a positive correlation was established between the CCT and the density of the corneal endothelium ( $r = 0.26$ ,  $p < 0.01$ ). In PES patients, a negative correlation was found between the percentage of hexagonal cells and the level of polymegethism ( $r = -0.37$ ,  $p < 0.01$ ) (see Table 6).

## DISCUSSION

Currently, in clinical practice, several types of non-contact endothelial microscopes from various manufacturers are used. The use of these microscopes, which are safe for the patient, enables ophthalmologists to accurately assess the endothelial layer of the cornea. Each of these tools has its own technological aspects and software as well as the ability to operate in automatic and/or semi-automatic modes, which is ultimately reflected in the digital values and repeatability of the examination results [23–27]. In our study, the morphology of the corneal endothelium was assessed using a non-contact endothelial microscope (EM 935, Haag-Streit AG, Köniz, Swit-

zerland) in semi-automatic mode. The EM 935 is a portable device installed on a slit lamp (BQ 900, Haag-Streit AG, Köniz, Switzerland) that enables ophthalmologists to analyze ECs in automatic and semi-automatic modes. In their work, Y. Goldich et al. (2010) showed that the EM 935 in semi-automatic mode provides higher repeatability and quality of research [25].

Of neuroectodermal origin, the corneal endothelium (posterior epithelium) is a metabolically active layer of cells involved in the regulation of fluid and the transport of dissolved matter between the aqueous humor and the stroma components. Similar to other organs and tissues of the human body, the cornea is subject to age-related changes, and the repair capabilities of ECs have certain limitations [28].

With continuous rapid growth of the cornea in the prenatal period, in the early stages of pregnancy, there is a sharp increase in the number of ECs due to mitosis, whereas, in the later stages of pregnancy, there is an increase in the area of ECs without a significant change in their number. Accordingly, at the time of birth, the endothelium density decreases from 16,015 to 6167 cells/mm<sup>2</sup>. Further, the absence of proliferation and the age-related loss of ECs usually determine a decrease in endothelium density over the course of a person's life [29]. S. Galgauskas et al. (2013), when examining patients of European origin aged 20–89 years (358 eyes), found that patients without ophthalmologic pathology had an age-related decrease in the density of ECs from an average of 2,931 ( $SD = \pm 371$ ) cells/mm<sup>2</sup> at the age

of 20–29 years to 2,222 ( $SD = \pm 182$ ) cells/mm<sup>2</sup> at the age of 80–89 years. At the same time, scientists revealed a strong negative correlation between age and EC density ( $r = -0.65$ ,  $p < 0.01$ ) and a direct correlation between EC size and age ( $r = 0.586$ ,  $p < 0.01$ ). However, no correlation was found between age and polymegethism or between age and hexagonal factor of the corneal endothelium [23]. According to different researchers, the average density of the corneal endothelium in healthy representatives of the European population older than 50 years is 2,200–2,600 cells/mm<sup>2</sup> [23, 24, 26, 30]. In addition, in the population older than 70 years, the risk of decreasing EC density to 2,000 cells/mm<sup>2</sup> increases. This value is considered to be the limit below which the corneal endothelium loses the ability to perform its functions normally, and when the number of cells is below 500 cells/mm<sup>2</sup>, the risk of corneal edema significantly increases [28, 31].

The results of our study showed that the presence of PES, particularly PEG, determines the decrease in EC density in patients of the studied groups. In addition, a decrease in EC density compared with the control group was also observed in POAG patients ( $p < 0.05$ ). In this case, the lowest EC density was noted in patients with advanced PEG stages ( $p = 0.001$ ). It should also be noted that when comparing this index in patients with PES and PEG who have varying severities of pseudoexfoliation syndrome, the minimum value was also observed in PEG patients with significant PES manifestations ( $p < 0.05$ ). Further, in patients with PES without glaucoma, no significant differences were found depending on the degree of its manifestation ( $p > 0.05$ ). In our study, the minimum EC density value was recorded in a 72-year-old patient with advanced PEG and pronounced PES manifestations (793 vs. 1,558 cells/mm<sup>2</sup> for the control group, 1,888 cells/mm<sup>2</sup> for the POAG group, and 1,690 cells/mm<sup>2</sup> for the PES group). The data obtained coincide with the results of previous studies and confirm the hypothesis that a decrease in pigment epithelial cells can be associated both with the progression of PES manifestations and with the development of the glaucomatous process, and these factors can act independently of each other [13–15].

It is believed that an increase in the intraocular pressure and its fluctuations, activation of proteases (in particular, matrix metalloproteinases), changes in levels of transforming growth factors, and proinflammatory cytokines in the anterior segment of the eye contribute to increased apoptosis processes and reduced viability of endotheliocytes in glaucoma [32–34]. Regardless, both ischemia and oxida-

tive stress observed in PES and the immunological activity of PEM itself can influence the quantitative and qualitative indicators of the morphology of the corneal endothelium [12, 35–37].

It is well known that hexagonal cells are normal representatives of the corneal endothelium. Usually, by the time of birth, the corneal endothelium is represented mainly by cells having a hexagonal configuration, which are identical in size and evenly distributed over the entire posterior surface of the cornea, and by the age of 30, the percentage of these cells is reduced to approximately 70% [29]. Hexagonal cells, which are closely interconnected and form a kind of network, provide stability and constancy of the endothelial layer in stretching, especially when EC density decreases, and also create a barrier against penetration of aqueous humor from the anterior chamber, thereby maintaining the stroma in a state of relative dehydration and ensuring accuracy of light penetration through the layers of the cornea [38]. It is believed that in a healthy cornea in an adult, its content should be at least 60% [23, 24, 26].

Data on the possibility of reducing the percentage of hexagonal cells in patients with PEG, POAG, and PES are contradictory. Some authors have found a decrease in the percentage of hexagonal cells and an increase in the level of pleomorphism in patients with PEG and POAG [13, 15, 16]. No other differences in these parameters were found [14, 39]. We did not reveal differences in the percentage of hexagonal cells among patients of the studied groups ( $p > 0.05$ ). However, it should be noted that all values in patients of this age group were in the pathology zone, namely less than 60% ( $48.4 \pm 1.3\%$  for HC,  $44.9 \pm 0.8\%$  for PEG,  $47.3 \pm 1.2\%$  for POAG, and  $47.4 \pm 1.3\%$  for PES).

As mentioned, the lack of proliferation of ECs in adults and a decrease in EC density with age require compensatory replacement, which consists of an increase in the size and shape of ECs [29]. Polymegethism reflects the presence of cells of different sizes in the cell population studied. With age, a physiological insignificant increase in the variation coefficient of the cells is noted. However, the level of polymegethism in the norm should not exceed 30% [23, 24, 26]. Consequently, given the data on the decrease in EC density in patients with PEG and POAG, we can expect to observe an increase in the level of polymegethism.

The results of our study showed an increase in the percentage of polymegethism in the PEG and POAG groups compared to the control group ( $p < 0.01$ ). The values of this index in PES patients did not significantly differ from the control group but were lower

than that in PEG patients ( $p < 0.05$ ). It should be noted that the level of polymegethism in the control group also exceeded the age norm ( $46.5 \pm 2.7\%$ ). When evaluating polymegethism in patients with PEG and POAG, depending on the stage of glaucoma, it was found that in patients with advanced PEG stages, this indicator was significantly higher than in patients with initial stages of the process ( $66.8 \pm 3.0\%$  and  $56.3 \pm 2.0\%$ ,  $p < 0.01$ ), and was not registered in the group of patients with different stages of POAG. It should be noted that patients with PEG and more pronounced manifestations of PES had the highest level of polymegethism ( $p = 0.01$ ). In PES patients, no differences in this parameter related to the severity of the manifestations of the syndrome were identified.

The available data on the presence of changes in cell size in PEG, POAG, and PES are ambiguous [13–16, 39]. This is probably due to the characteristics of the instruments used and to size, ethnic, and age characteristics of the samples as well as other factors. Based on the results of our work, the significant impact of both glaucoma and the severity of PES manifestations on the level of polymegethism was considered in the groups studied.

It is known that with age, the CCT decreases. Scientists have also found a negative correlation between CCT and age [23, 24]. In addition, the presence of a thin cornea may be one of the risk factors for glaucoma [40]. The results of recent studies have shown that patients with PES and PEG can also be characterized by a decrease in the CCT. In most of these patients, a statistically significant decrease in CCT index was shown in patients with PEG compared to those with PES [15, 18, 19]. However, there is evidence of the absence of significant differences in this parameter in the preceding patient groups [14, 16, 41]. Moreover, there is evidence that severe PES manifestations with pronounced morphological changes are associated with thickening of the central corneal zone. It is assumed that an increase in CCT in PES and PEG may be associated with an uneven thickening of the Descemet's membrane and impaired pumping function of the endothelium, which may lead to an increase in hydration of the cornea [10, 13, 42]. The results of the CCT examination in patients with POAG are also ambiguous [15, 16].

In the course of our study, a significant decrease in the CCT was revealed in the group of PEG patients compared to the control group ( $546.3 \pm 2.6 \mu\text{m}$  and  $555.7 \pm 4.1 \mu\text{m}$ ,  $p < 0.05$ ). In addition, a thinner cornea was detected in patients in the advanced stages of PEG compared to patients in the initial stage

( $p < 0.05$ ). In patients with POAG and PES, there was no significant difference in CCT as compared to the control group and as related to the stage of glaucoma or PES severity ( $p > 0.05$ ). There were also no differences when comparing this parameter between the PEG, POAG, and PES groups ( $p > 0.05$ ). It is believed that a decrease in the CCT in PES and PEG may be associated with a decrease in EC density and a decrease in the density of the anterior and posterior keratinocytes as well as the basal epithelium layer. In addition, there is a possibility that detecting PEM in the cornea may induce apoptosis of keratocytes and deterioration of the structure of the extracellular matrix [11–13]. The importance of detecting a subtler CCT in PEG patients, including in our study, consists of the possibility of underestimating intraocular pressure values and therefore increasing the risk of untimely diagnosis of glaucoma in PES.

We expected that the indices obtained in assessing polymegethism would have a negative feedback with the EC density indicator. In the studied groups and in the control group, there were indeed strong negative correlations between ED and percentage of polymegethism ( $r = -0.85$ ,  $p < 0.01$  for control group;  $r = -0.87$ ,  $p < 0.01$  for PEG;  $r = -0.86$ ,  $p < 0.01$  for POAG;  $r = -0.73$ ,  $p < 0.01$  for PES). However, negative correlations between the percentage of hexagonal cells and the level of polymegethism were only observed in PEG patients ( $r = -0.37$ ,  $p < 0.01$ ). Mild positive correlations between the percentage of hexagonal cells and ED were recorded in the PEG and PES groups ( $r = 0.16$ ,  $p < 0.05$  and  $r = 0.29$ ,  $p < 0.05$ , respectively).

When assessing the state of the ICA in patients with PEG and PES, the prevalence of exogenous and mixed pigmentation was established ( $p < 0.01$ ), with the greatest pigmentation intensity detected in PEG patients ( $p < 0.01$ ). Our data are consistent with the results of DjordjevićJocic et al. (2012) [43]. In addition, the authors found a positive correlation between the levels of matrix metalloproteinase-2 and transforming growth factor- $\beta$ 1 in the anterior chamber fluid and the degree of pigmentation of ICA ( $r = 0.36$  and  $r = 0.31$ ,  $p < 0.05$ ) in PEG patients, which is consistent with data on the participation of these substances in the development of PES and PEG [33]. It should be noted that patients with PEG and to a lesser extent PES had the most pronounced dystrophic changes in the iris ( $p < 0.01$ ), which confirms the data on the involvement of the tissues of the iris in the pathogenesis of PES [2, 44].

In addition, we evaluated the possible influence of IOP-lowering eye drops of known groups

(carbonic anhydrase inhibitors, prostaglandin analogs,  $\beta$ -blockers,  $\alpha_2$ -adrenoceptor agonists) and their combinations on the parameters of the corneal endothelium. In our study, no reliable data were obtained on the potential of such an impact ( $p > 0.05$ ).

## CONCLUSION

1. In patients with PES and, to a greater extent, PEG, significant changes in the morphology of the corneal endothelium were revealed (decrease in the density of ECs, increase in the percentage of polymegethism).
  2. The severity of changes in PEG patients was associated with the severity of the glaucomatous process and PES manifestations.
  3. In PEG patients, the most pronounced dystrophic changes in the iris and the intensity of ICA pigmentation were registered.
  4. Patient use of IOP-lowering eye drops and their combinations did not have an effect on corneal endothelium morphology.
- There is no conflict of interest.

### Authors' contribution:

The concept and design of the study were implemented by *I.S. Beletskaya* and *S.Yu. Astakhov*.

Collection and processing of materials were performed by *I.S. Beletskaya* and *N.V. Tkachenko*.

Analysis of the data obtained and writing of the text were performed by *I.S. Beletskaya* and *S.Yu. Astakhov*.

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