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Corneal Changes in A Sample of Pseudoexfoliation Iraqi Patients

Ahmed M. Rasheed[1] *CABHS*, **Diyar J. Kadum**[2] *CABHS, FICO*

[1]Dept. of Surgery, College of Medicine, Al-Nahrain University, Baghdad, Iraq, [2]Ibn Al-Haitham Teaching Eye Hospital, Baghdad, Iraq

Abstract

Background Pseudoexfoliation syndrome is a common eye disorder that can affect different parts of the eye causing significant morbidity.

Objective To compare corneal endothelial changes between patients with pseudoexfoliation syndrome and normal age matched patients.

Methods Specular microscopy was used to measure central corneal thickness, average size of endothelial cells and coefficient of variation in cell area, endothelial cell density, as well as hexagonality of 238 eyes from 238 patients (120 eyes from patients with pseudo exfoliation syndrome and 118 eyes from normal age-matched patients).

Results Patients with pseudoexfoliation syndrome had lower central corneal thickness (p value 0.049) compared to the control (491.6±28.86 vs 502.5±35.77 µm), lower endothelial cell density (p value 0.02) compared to control (2458.9±430.8 vs 2585.3±378.8 cell/mm^2), lower hexagonality (P value 0.006) compared to control (48.25±18.76 vs 55.06±12,44), also a significantly higher coefficient of variation (p value 0.046) compared to control (36.15±7.381 vs 33.4±6.22).

Conclusion Pseudoexfoliation syndrome is associated with a significant change in the corneal endothelium, including reduction of endothelial cell density, increased variation of cells shape (pleomorphism) and increased variation of cells area (polymegathism). There was a significant change of central corneal thickness.

Keywords Corneal endothelium, specular microscopy, pseudoexfoliation syndrome, central corneal thickness

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List of abbreviations: CCT = Central corneal thickness, CD = Endothelial cell density, CV = Coefficient of variation, HEX =Hexagonality, PEX = Pseudoexfoliation syndrome

Introduction

The corneal endothelium is the inner layer of the cornea that is in contact with the aqueous humor in the anterior chamber of the eye. It consists of a single layer of cuboidal cells that are linked to each other by desmosomes and hemidesmosomes [(1)]. When cells are viewed from the posterior surface, there is an overall hexagonal pattern. The number of endothelial cells fall steadily with age and there is increased variation of cell size. The adult mean cell density is about 2500 cell /square mm, and this number falls gradually with age and it is estimated that between the ages of 20 and 80 years the reduction in cell density averages 0.52% per year [(2)].

The maintenance of a transparent cornea depends upon the endothelium producing a state of relative stromal dehydration [(3)]. The proteoglycan matrix that surrounds each collagen fiber of the stroma produce an imbibition pressure (60 mm hg), which tends to draw water into the cornea. Tight junctions between epithelial cells of the cornea form a

barrier to reduce the flow of water from the tear film into the stroma, but the absence of tight junctions between endothelial cells permits the free flow of aqueous into the stroma. If this water is allowed to accumulate it produces stromal swelling and clouding. The pump-leak concept of corneal hydration proposes that there is a dynamic equilibrium between the tendency of the stroma to swell and the active transport of ions by the endothelial pump to oppose the inward movement of water [4].

The normal function of the endothelial pump of the cornea may be affected by diseases that involve the endothelium like pseudoexfoliation and endothelial dystrophy.

Pseudoexfoliation syndrome (PEX) is an idiopathic age-related systemic disease manifesting itself primarily in the eyes [5]. It is diagnosed clinically by the deposition of abnormal fibrillar material on various intraocular structures including the corneal endothelium, anterior lens surface, iris, trabecular meshwork, zonules, and ciliary body [6]. This may lead to various ocular complications such as chronic open-angle glaucoma, lens subluxation, poor mydriasis and zonular dehiscence, capsular rupture or vitreous loss [7,8]. Corneal endothelial changes have also been reported [9,10], and this can affect the corneal hydration, thickness, and transparency. In patients with PEX, quantitative and qualitative morphological changes of the corneal endothelium have been demonstrated in specular and electron microscopic studies [9,11-13]. These changes represent an abnormal or unstable endothelium, predisposing to an endotheliopathy that may be more susceptible to the effects of intraocular surgery [9,14].

The aim of this study is to study the corneal endothelial changes in patients with pseudoexfoliation syndrome and to compare them with normal aged match subjects.

Methods

Two hundred thirty-eight eyes were examined, 120 eyes of patients with PEX and another 118 eyes of normal aged match subjects. Informed verbal consent was obtained from all patients. Exclusion criteria included patients with PEX glaucoma, previous ocular surgery or trauma, eye inflammation, corneal dystrophy, and metabolic disease like diabetes. Each eye was examined by slit-lamp for the anterior segment, intraocular pressure by Goldmann tonometry, and optic nerve head examination by non-contact volk magnifying lens +90. Specular microscopy then was done by non-contact Topcon sp-3000 p. For each eye 100±20 endothelial cells were counted in each image for analysis, and the following measurements were determined: Central corneal thickness, cell density, coefficient of variation, and hexagonality. Data were divided into four groups according to patients age as follows: Group A for those between 50-59 years; group B for those between 60-69 years; Group C for those between 70-79 years; and Group D for those more than 80 years. T test was used to assess the differences in mean for continuous variables, while chi square test was used to assess the differences in mean for continuous variables, while chi square test was used to assess the differences in distribution of categorical variables. Statistical analysis was performed using SPSS software windows version 21 and Student's independent t-test to reveal any significant association.

Results

There were 238 cases included in this study. Mean age of patients and control did not differ (for patients = 66.28±7.45 years and for control = 66.25±7.47 years), male to female ratio in the patient group was 1.66:1 while in the control group it was 1.45:1, so there is male predominance in both control & patient group (Tables 1 & 2).

By comparing central corneal thickness (CCT) between control corneas, patient's cornea, there is a significant decrease of mean CCT for patient group, mainly for age groups A, B, C except D where there is no significant difference in CCT (Table 3).

Table 1. Baseline characteristics of the study group

Age groups	Gender	Control		Patient	
		No.	%	No.	%
Group A	Male	12	17.1	12	16.0
	Female	11	22.9	11	24.4
Group B	Male	30	42.9	33	44.0
	Female	21	43.8	17	37.8
Group C	Male	23	32.9	26	34.7
	Female	15	31.3	15	33.3
Group D	Male	5	7.14	4	5.3
	Female	1	2.08	2	4.4
Total	Male	70	100	75	100
	Female	48	100	45	100

Table 2. Descriptive of age group (control and patient)

	Control		Patient		t-test	P-value	Sig.
Age groups	Mean	SD	Mean	SD			
Group A	55.8	2.92	56.2	2.72	0.405	0.689	NS
Group B	64.3	2.37	63.8	2.45	1.174	0.246	NS
Group C	72.6	2.48	72.4	2.36	0.462	0.646	NS
Group D	82.3	1.86	83.3	1.86	0.889	0.415	NS

*P>0.05 Non-significant

Table 3. Descriptive of central corneal thickness

	Control		Patient		t-test	P-value	Sig.
Age groups	Mean	SD	Mean	SD			
Group A	512.3	31.3	494.8	38.09	2.475	0.022	S
Group B	497.2	34.5	491.3	21.23	2.477	0.029	S
Group C	507.9	35.86	492.3	31.07	2.464	0.018	S
Group D	477.2	49.75	476.3	26.65	1.982	0.058	NS

*P<0.05 Significant, **P>0.05 Non-significant

Endothelial cell density (CD) significantly decreases for patient group in comparison with the control group, also it is only for group A, B, C while in group D there are no significant changes in endothelial cell count in comparison with the control group (Table 4).

With Regard to the percentage of hexagonal cells (hexagonality), there is a significant reduction in the mean of the patient group for age group A, B, C in comparison with the control group while group D shows nonsignificant reduction in hexagonality in comparison to control group (Table 5).

Table 4. Descriptive of central corneal thickness

Age groups	Control		Patient		t-test	P-value	Sig.
	Mean	SD	Mean	SD			
Group A	2701.1	184.3	2445.9	469.5	2.2624	0.015	S
Group B	2608.5	351.4	2565.1	470.2	2.047	0.049	S
Group C	2538.8	474.8	2369.4	358.9	2.323	0.047	S
Group D	2238.2	276.8	2236	99.7	1.892	0.092	NS

*P<0.05 Significant, **P>0.05 Non-significant

Table 5. Descriptive of hexagonality

Age groups	Control		Patient		Z-test	P-value	Sig.
	Mean	SD	Mean	SD			
Group A	59.8	7.71	47.4	22.48	2.409	0.025	S
Group B	56.47	9.83	49.54	17.1	2.453	0.018	S
Group C	53.57	13.74	49.0	19.27	2.021	0.049	S
Group D	34.0	17.84	33.16	2.639	1.72	0.145	NS

*P<0.05 Significant, **P>0.05 Non-significant

As for Coefficient of variation (CV), there is increased variation in individual cell areas for all age groups for the patient group in comparison to the control group as shown in the table 6:

Table 6. Descriptive of coefficient of variation control and patient

Age groups	Control		Patient		Z-test	P-value	Sig.
	Mean	SD	Mean	SD			
Group A	32.4	4.74	35.03	7.28	2.043	0.049	S
Group B	33.9	6.698	36.09	5.994	3.012	0.035	S
Group C	32.95	6.407	36.36	9.02	2.39	0.041	S
Group D	34.6	6.804	39.5	6.31	2.422	0.045	S

*P<0.05 Significant

In comparison with non PEX control corneas, PEX corneas (patient group) have lower central corneal thickness (CCT) (491.6 vs 502.5 µm), lower endothelial cell density and hexagonality (2458.9 vs 2585.3 cell/mm^2, 48.25 vs 55.06% respectively), a significant increase in endothelial cell size, standard deviation of cell size and coefficient of variation (CV) (36.15 vs 33.4) as shown in the table 7.

Corneal endothelial changes regarding gender distribution in both patient & control group. All data reveal a higher mean for male except for CV which is higher for female in both patient & control group (Table 8).

Table 7. Overall differences in corneal parameters between pseudoexfoliation patients and control

Parameter	Control		Patient		t-test	P-value	Sig.
	Mean	SD	Mean	SD			
Central corneal thickness	502.5	35.77	491.6	28.86	2.012	0.049	S
Endothelial cell density	2585.3	378.8	2458.9	430.8	2.365	0.02	S
Hexagonality	55.06	12.44	48.25	18.76	2.772	0.006	S
Coefficient of variation	33.4	6.22	36.15	7.381	2.136	0.046	S

*P<0.05 Significant

Table 8. Corneal parameters difference between pseudoexfoliation patients and control with regards to gender

Parameter	Gender	Control		Patient		t-test	P-value	Sig
		Mean	SD	Mean	SD			
Central corneal thickness	Male	509.2	37.25	501.04	36.2	2.322	0.047	S
	Female	492.8	31.38	500.2	34.25	2.143	0.034	S
Endothelial cell density	Male	2595.7	381.9	2484.9	439.9	2.696	0.008	S
	Female	2569.9	377.7	2433.1	417.3	2.773	0.004	S
Hexagonality	Male	56.08	13.23	50.37	18.62	2.033	0.047	S
	Female	53.58	11.16	47.02	18.53	2.354	0.046	S
Coefficient of variation	Male	32.07	5.951	33.51	5.84	1.89	0.089	NS
	Female	35.22	6.21	36.3	9.96	1.99	0.065	NS

*P<0.05 Significant, **P>0.05 Non-significant

Discussion

The pseudoexfoliation syndrome affects all structures of ocular anterior segment. By electron microscopy, large clumps of typical pseudoexfoliation material can be found adhering to the corneal endothelium, and masses of pseudoexfoliation material are incorporated into the posterior Descemet membrane [12]. These may lead to early corneal endothelial decompensation. In this study, we found that the thinnest corneas occur in the eyes of patients with PEX (P<0.049) and this was similar to the result found by Inoue et al [15] and Yazgan et al. [16] in their study of corneal biomechanical comparison of PEX, pseudoexfoliative glaucoma and healthy subjects. They found that the mean CCT were 546.3± 28, 525.5±35 and 509±36 µ, in healthy subjects, PEX and PEXG, respectively. The differences on CCT were also significant among the three groups ($p < 0.001$). However, Hepsen et al. [17] and Arnarsson et al. [18] reported that patients with PEX have a higher CCT than the control group. (P=0. 56, P= 0. 23, respectively) but these results are statistically non-significant.

Interesting conclusions regarding the influence of PEX on the corneal stroma were included in the study published by Zheng et al. [19]; the authors, using confocal microscopy, identified deposits of pseudoexfoliating materials in the cornea itself. They also showed that the number of keratocytes in the corneal stroma of the eyes of patients with PEX (per unit of area) was smaller than in the group of people without PEX. They concluded that the presence

of the pseudoexfoliating material induces apoptosis of corneal stroma keratocytes and in the end leads to the impoverishment of its extracellular structure. This may result in the thinning of the cornea and its greater susceptibility to elevated intraocular pressure.

The normal density of corneal endothelial cells in adults is approximately 2500 cells/mm^2 and it is reduced by about 0.6% a year so normally endothelial cell density decreases with age. In this study, it was found that there is a significant reduction of endothelial cell density in eyes with PEX in comparison with normal aged match eyes (p = 0.02). This finding was similar to reported studies by Miyake et al. [9]; Zheng et al. [19]; Yüksel et al. [20]; Tomaszewski et al. [21]; Wang et al. [22]; Quiroga et al. [23]; Kovaliunas et al. [24].

Research presented above clearly shows that PEX significantly influences cell density of corneal endothelium of people with this disease. The cause of the lower endothelial cell density of patients with PEX is the pseudoexfoliation material, appearing at the earliest stages of PEX, which settles on the endothelium penetrating it in the direction of the Descemet's membrane and breaking the connections between individual six-sided cells, which results in local accelerated apoptosis of these cells. Other factors recognized by researchers, excluding the accumulation of PEX material causing the reduction of the number of cells within the layer of the corneal endothelium, include hypoxia of the anterior chamber, changes in the fibroblasts of the endothelium, and elevated concentration of TGF-α1 [6].

The average size and coefficient of variation (CV) of corneal endothelial cells were found to be significantly increased in eyes with PEX (P<0.046). The increase in coefficient of variation (CV) indicates the presence of polymegathism in which endothelial cells enlarge to fill the gaps between adjacent cells. This study also showed that the percentage of hexagonal cells were significantly reduced (P<0.006), indicating the presence of pleomorphism. These results were similar to those obtained by Miyakeet al. [9]; Yüksel et al. [20]; and Wali et al. [25].

However, Inoue et al. [15] and Wang et al. [22] found that the difference of coefficient of variation of cell size and percentage of hexagonal cells between the PEX eyes and the control eyes was not statistically significant.

Another aspect of the study result is the fact that this syndrome is strongly age-related. In this study, the age factor was evident. Despite the bulk of our study depend on Group B but we found that Group A is more affected by pseudoexfoliation syndrome than others, in addition to that, for patients older than eighty there are no significant changes apart from polymegathism in comparison with the control group.

These observations suggest that the corneal endothelial changes represent a consistent finding in eyes affected with pseudoexfoliation.

This study concluded that there is a decrease in corneal endothelial cells in patients with pseudoexfoliation syndrome, in addition to pleomorphism, polymegathism and corneal thinning.

The authors recommended that ophthalmic surgeons should pay special attention while doing surgery in eyes with pseudoexfoliation, and this may include doing preoperative endothelial cell study by specular microscopy to detect eyes at risk of endothelial decompensation.

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Authors contribution

Dr Rasheed: collection of study cases. Dr Kadum: collection of study cases and writing of the article.

Conflict of interest

Authors declare no relation with any institute or personal that have any influence on the results of this study.

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Correspondence to dr. Ahmed M. Rasheed
E-mail: Amj1970a@yahoo.com
ahmedmajeed@colmed-alnahrain.edu.iq
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