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Quantitative and Qualitative Corneal Endothelial Morphology of Omani Patients with Pseudoexfoliation Syndrome

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وضع خلايا بطانة قرنية العين لدى المرضى العمانيين المصابين بمتلازمة التقشر الكاذب لعدسة العين

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الملخص: الهدف: تعتبر متلازمة التقشر الكاذب لعدسة العين السبب الرئيسي المؤدي إلى الإصابة بالماء الأزرق الثانوي والعمى . حيث أن العين المصابة بتلك المتلازمة وما يرافقها من تغيرات في خلايا بطانة القرنية قبل العملية قد تؤدي إلى تدهور القرنية بعد العملية. **الطريقة:** في هذه الدراسة المقطعية تم دراسة 126 عينا ل 69 حالة (43 ذكرا و 26 أنثى) قبل إجراء عملية نزول الماء الأبيض في قسم أمراض العيون بمستشفى جامعة السلطان قابوس في الفترة بين 2003 إلى 2005 ميلادية. كل المرضى تم فحصهم بواسطة مجهر العين الحيوي الدقيق. **النتائج:** بلغ متوسط عمر المرضى المصابين بمتلازمة التقشر الكاذب لعدسة العين 63.2 عاما. أظهرت 108 عينا (85.7%) تعدادا طبيعيا في خلايا بطانة العين (1650-3500/ملم^2). أما بالنسبة لنوع الخلايا فقد كان غير طبيعي بصورة كبيرة من ناحية اختلاف حجم الخلايا وتعدد أشكالها. فقد كان تعداد خلايا البطانة ل 12 عينا أعلى من المستوى الطبيعي في تلك الفئة العمرية . بينما كان التعداد أقل من المستوى الطبيعي ل6 عيون. كما كان متوسط تعدد أشكال الخلايا أعلى بشكل ملحوظ عن الوضع الطبيعي . بينما كان حجم الخلايا أقل من المستوى الطبيعي. كانت العلاقة بين حجم وتعدد أشكال الخلايا كبيرا في المرضى الذكور مقارنة بالإناث . كما كان كبيرا للمرضى الذين تتعدى أعمارهم 60 عاما. كما كانت هذه العلاقة كبيرة أيضا بين الفئة المصابة بالماء الأزرق مقارنة بالمرضى غير المصابين. **الخلاصة:** تبين هذه الدراسة أن تدهور القرنية للعين المصابة بمتلازمة التقشر الكاذب يمكن أن يظهر علامات غير طبيعية في حجم الخلايا وفي تعدد أشكالها حتى وان كان تعداد الخلايا طبيعيا.

مفتاح الكلمات: متلازمة التقشر الكاذب لعدسة العين . تعدد أشكال خلايا بطانة العين . حجم خلايا بطانة العين . مجهر العين الدقيق.

ABSTRACT ***Objective:*** Pseudoexfoliation (PEX) syndrome is one of the leading causes of secondary open angle glaucoma and blindness. This study explored whether in PEX eyes, preoperative changes in corneal endothelial cell morphology might be a risk factor for postoperative corneal decompensation. ***Methods:*** One hundred twenty six eyes of 69 preoperative cataract patients (43 males, 26 females) were enrolled in this cross-sectional study from the Ophthalmology Department at Sultan Qaboos University Hospital between 2003-2005. All patients were subjected to confocal biomicroscopy. ***Results:*** The mean age of patients with PEX eyes was 63.2 years. One hundred and eight (85.7%) eyes with PEX had endothelial cell counts within the normal range (1650-3500/mm^2). The qualitative morphology of the endothelium of PEX corneas was highly abnormal in term of polymegathism and pleomorphism. Twelve eyes had endothelial cell counts higher than normal for that age group. Only 6 eyes had endothelial cell counts lower than normal. The mean value for the pleomorphism was found to be significantly lower than normal and for polymegathism significantly more than normal. The relationship between pleomorphism and polymegathism was stronger for males than for females and stronger for patients under 60 years than patients over 60 years. The same relationship between pleomorphism and polymegathism showed a stronger relationship for the glaucoma group as compared to the non-glaucoma group. ***Conclusion:*** This study revealed that corneal decompensation in PEX eyes can occur in presence of abnormalities in polymegathism and pleomorphism, even when the endothelial cell counts may be normal.

Key Words: Pseudoexfoliation; Pleomorphism; Polymegathism; Confoscan.

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Advances in Knowledge

- Ocular Pseudoxfoliation syndrome induces structural changes in the morphology of the cornea that directly reflects the high risk of postoperative corneal decompensation.
- Confocal scans can help the surgeon predict this possibility and so properly counsel the patient prior to the surgery.
- This can make postoperative management more specific and result oriented.

Application to Patient Care

- The study shows the importance of confocal biomicroscopy in ocular pseudoexfoliation syndrome.
- Patient care can be more predictive and specific if the corneal status is known preoperatively.
- This can make postoperative management more specific and result oriented.

Since 1917 when the Finnish ophthalmologist Lindberg first described the pseudoexfoliation (PEX) syndrome, the main intraocular production sites of PEX material have been identified as the epithelial cells of the lens capsule, the iris, the non-pigmented ciliary epithelium, and the trabecular meshwork, as well as the corneal endothelial cells.[1] Since PEX is also associated with hypoxia of the anterior segment, it seems pertinent to acquire more knowledge of the *in vivo* morphology of corneal endothelial cells in addition to the existing histopathological features in order to predict problems for intraocular surgery in these eyes. The PEX syndrome is a systemic disease with mainly ocular manifestations.[1] Its most common systemic manifestations include ischaemia, infarctions and strokes involving the myocardium, bowels and intracranial structures. Epidemiologically, PEX has a wide geographical distribution with the highest incidence in countries prone to ultra-violet light, in northern latitudes and at high altitudes.[2, 3]

The prevalence of PEX is variable: USA (1.6%), Germany (4.0%), England (4.7%), France (5.5%), Norway (6.3%), Saudi Arabia (13%), Finland (20%), and Iceland (25% - in more than 60 years of age). The risk of developing glaucoma in PEX is 20-77%.[1, 4] Aasved found a nine fold increase in prevalence of PEX in first degree relatives over age of 40 years compared to the general population, suggesting an autosomal dominant inheritance.[5]

This study was commenced with the aim of highlighting the importance and need for preoperative evaluation of corneal endothelial cells in PEX eyes in the Omani population undergoing cataract, or other intraocular anterior segment surgery.

METHODS

A total of 69 adult patients (43 males and 26 females) and 126 eyes (78 male eyes and 48 female eyes), who met the inclusion and exclusion criteria, were enrolled in this study. The inclusion criterium was patients aged 40 years and above. Eyes with any other corneal pathology or prior surgery that would prevent reliable confocal microscopy were excluded.

All patients were subjected to refraction, applanation tonometry, slit-lamp biomicroscopy, gonioscopy and fundus examination. Eyes confirmed to have PEX on the anterior lens capsule, iris and/or endothelium before or during mydriasis were subjected to a confocal microscopic examination (Confoscan 2, Nidek Japan). Patients diagnosed with glaucoma were examined by frequency-doubled perimetry (Matrix^{R}, Zeiss-Humphrey), Humphrey automated perimetry and OCT 2 papillometry (OCT 2 Nidek).

Confocal biomicroscopy was done under topical anesthesia (benoxinate 0.4%) using sterile transparent gel as a coupling medium.

The confocal microscopy outcome of corneal endothelium was assessed in terms of endothelial cell count, polymegathism and pleomorphism. The endothelial cell count was calculated on the basis of a sample size which was different for different eyes and compared with age-matched mean values for other studies in the normal population.

The pleomorphism and polymegathism values were defined against normal values of >59.0 for pleomorphism and <30.0% for polymegathism, which means that a normal healthy cornea should have at

Table 1: ***Characteristics of 126 PEX eyes***

	Males (78)	Females (48)	Total (126)	PEX with Glaucoma (48)	PEX with no Glaucoma (78)
Age	63.45 ± 7.40 (49 - 84)	62.77 ± 7.85 (41 - 76)	63.19 ± 7.55	60.81± 8.33 (41 - 84)	64.65 ± 6.67 (49 - 76)
Endothelium	2463.18 ± 485.28 (1579 - 3974)	2470.2± 544.9 (1595 - 4239)	2465.9 ± 506.7	2438.0 ± 503.4 (1579 - 3974)	2483.0 ± 511.2 (1595 - 4239)
Pleomorphism	34.70 ± 11.90 (7.70 - 69.80)	34.52 ± 12.12 (16.2 - 59.8)	34.63 ± 11.92	37.09 ± 12.43 (16.2 - 65.4)	33.12 ± 11.44 (7.7 - 69.8)
Polymegathism	57.89 ± 15.66 (28.3 - 103.5)	60.10 ± 18.14 (30.7 - 105.1)	58.73 ± 16.61	59.69 ± 16.79 (30.0 - 105.1)	58.14 ± 16.58 (28.3 -105.1)

Each cell display; Mean ± SD and (Minimum value, Maximum)

least 60% endothelial cells with regular shape or hexagonality and should not have abnormal endothelial cell sizes or areas (normal 312-320 micron square) in more than 30% of cells.

The Statistical Package for the Social Scienes (SPSS software, Version 10) was used for the analysis of the data and to make the figures. The Student's t-test was applied to test the significance difference between the means of the groups for the variables under study and the chi-square test was used to compare the categorical variables. A *p*-value of .05 or less was taken as significant. Selection of the type of regression curve is based on the R^2-values for different types of regression [Table 4]. A higher degree curve was preferred only when the difference in R^2 -values was significant.

RESULTS

Sixty nine patients (43 males, 26 females), with 126 eyes diagnosed to exhibit ocular PEX on slit-lamp biomicroscopy, were selected for morphometric analysis of corneal endothelium by Confoscan 2 (Nidek). All the patients were of Omani origin.

The patient characteristics were as follows, [Table 1]: The mean age of the patients was 63.45 ± 7.40 years for males and 62.77 ± 7.85 years for females. Of 126 PEX eyes the majority of patients (42.9%) belonged to age group 61-70 years, followed by 38.1% in 51-60 years age group, 15.9% in >70 years age group and 3.2% aged <50 years. The mean age for patients with PEX glaucoma was 60.81 years as compared to 64.65 years in patients with PEX without glaucoma, suggesting a younger age group for PEX glaucoma.

The endothelial cell count [Tables 1 & 2] was as follows: Seventy eight male PEX corneas had a mean endothelial cell counts of 2463.18 ± 485.28 cells/mm² compared to 2470.21 ± 544.93 cells/mm² for 48 female PEX corneas; this difference was not found to be statistically significant ($p = 0.942$). The overall mean endothelial cell count for all 69 patients with 126 PEX eyes was 2465.86 ± 506.68 cells/mm². The endothelial cell count of PEX eyes in this study was found to be within the normal range in 86.5%. Only 3.2% of PEX eyes had endothelial cell counts less than age-matched normal eyes. A total of 10.3% PEX eyes had endothelial cell counts that ranged even higher than that of age-matched control eyes. Most frequently (62 PEX eyes) the endothelial cell counts ranged between 2000-2500 cells/mm², and six eyes even had endothelial cell counts of more than 3500 cells/mm². The mean endothelial cell count for the PEX eyes with glaucoma (48) was 2438 ± 503.4 (1579-3974) compared to 2483 ± 511.2 (1595-4239) in PEX eyes without glaucoma (78); this difference was also not found to be statistically significant ($p = 0.629$).

As far as pleomorphism and polymegathism [Table 1 & 2] were concerned the following results were found. The pleomorphism (loss of hexagonality) data were abnormal in 122 PEX eyes (96.8%). Only four PEX eyes had pleomorphism of 60 and above (normal > 59.0%). Similar changes in cell density and hexagonality have been reported by Hatorri.[6]

Forty three PEX eyes had pleomorphism values in the range of 20-30. The mean pleomorphism for 126 eyes was 34.63% ± 11.92 (normal >59.0%). In spite of having slightly and statistically non-significant lower endothelial cell counts compared to females, the males showed better, though statistically non-significant, pleomorphism values (34.70% ± 11.90) compared to females (34.52% ± 12.12).

Table 2: ***Abnormal values/cells of different factors in 126 PEX eyes***

Factor	Normal	High	Low
Endothelium	108 (85.7%)	12 (9.5%)	06 (3.2%)
Pleomorphism	04 (3.2%)	Not applicable	122 (96.8%)
Polymegathism	02 (1.6%)	124 (98.4%)	Not applicable

The eyes with PEX glaucoma had more pleomorphism (37.09 ± 12.43) than eyes with PEX without glaucoma (33.12 ± 11.44) [Table 1].

Polymegathism was very frequent in 124 PEX eyes (98.4%) exhibiting abnormal size and area of endothelial cells (average area of a normal endothelial cell is 312-320μ²). The normal value for polymegathism is <30.0%. In this study, only two eyes had normal cell size/area, or had polymegathism <30.0%. The mean value for polymegathism in 126 eyes was 58.73% ± 16.61 (normal <30.0%). Females showed more abnormal values for polymegathism (60.10% ± 18.14) than males 57.89 ± 15.66), although it was not a statistically significant result.

Eyes with PEX glaucoma had more polymegathism (59.69 ± 16.79) than PEX eyes without glaucoma (58.14 ± 16.58) [Table 1]**;** however, this difference was not significant.

The quadratic relationship of pleomorphism on polymegathism displayed a strong inverse relationship. Classifying this relationship into different categories, it was observed that this relationship is stronger for males (R^2 = 0.638) than females (R^2 = 0.602).

The same association was found stronger in the under 60 years old age group (R^2 = 0.727) as compared to above 60 years old age group (R^2 = 0.581). Classifying the same relationship according to glaucoma versus non-glaucoma groups, it was observed that eyes with PEX glaucoma exhibit a stronger relationship (R^2 = 0.766) than PEX eyes without glaucoma (R^2 = 0.604), [Table 4].

However, the relationship between endothelium and polymegathism was not as strong as the relationship between pleomorphism and polymegathism. Even the cubic regression of endothelium on polymegathism did not exhibit a strong relationship for the same categories: gender groups: males (R^2=0.121) versus females (R^2 = 0.167); age groups: <60 years (R^2 = 0.129) versus > 60 years (R^2 = 0.129), and glaucomas: (R^2 = 0.142) versus non-glaucomas (R^2 = 0.121) [Table 4].

PEX-glaucoma eyes were then compared with non-glaucomatous eyes. The mean age of PEX patients with glaucoma (60.81 years ± 8.33) was found to be significantly lower than the mean age of the PEX patients without glaucoma (64.65 years ± 6.67, p = 0.005); also, among the ≤60 years old age group (52 eyes), 55.8% were glaucoma cases, compared to only 25.7% glaucoma cases among > 60 year old age group (74 eyes). This difference was also found to be statistically significant (p = .001), evidencing a trend for the predominance of PEX glaucoma in the younger age group, maybe due to earlier and better means of diagnosis**.**

PEX glaucoma seems more common among males (41%) than in females (33.3%), however, this difference was not found to be statistically significant.

The mean endothelial cell count for PEX glaucoma eyes (2438.0 ± 503.43 cells/mm²) was less than for non-glaucomatous PEX eyes (2483 ± 511.46 cells/mm²). Higher values for pleomorphism were found in eyes with PEX glaucoma (37.09 ± 12.43) compared to PEX eyes without glaucoma (33.12 ± 11.44). Polymegathism was slightly more prevalent (59.69 ± 16.79) in PEX

Table 3: ***Correlations and their significance***

Factors/variables	Pearson correlation	Significance
Endothelium versus Pleomorphism	- 0.246	p = .005
Endothelium versus Polymegathism	0.072	Not significant
Pleomorphism versus Polymegathism	- 0.683	p < .000001

Table 4: ***R2 values for different type of regression curves***

	Type of regression		
Regression curve of:	**Linear**	**Quadratic**	**Cubic**
Pleomorphism on Polymegathism	0.467	0.619	0.625
Males and Females	0.461 & 0.484	0.638 & 0.604	0.648 & 0.603
Age ≤ 60 yrs. and Age > 60 yrs,	0.586 & 0.406	0.725 & 0.573	0.727 & 0.581
Glaucoma and No glaucoma	0.643 & 0.402	0.765 & 0.604	0.765 & 0.623
Endothelium on Polymegathism	0.017	0.060	0.124
Males and Females	0.070 & 0.001	0.077 & 0.099	0.121 & 0.167
Age ≤ 60 yrs. and Age > 60 yrs.	0.010 & 0.038	0.039 & 0.075	0.129 & 0.129
Glaucoma and No glaucoma	0.002 & 0.036	0.068 & 0.065	0.142 & 0.121

glaucoma compared to PEX eyes without glaucoma (58.14 ± 16.58); the above mentioned differences were not found to be statistically significant [Table 1].

The statistical evaluation is shown in Table 2. According to Pearson's 2-tailed correlation significance, the following parameters revealed statistically significant values (p = .005 or p <.005):

1. Pleomorphism and polymegathism for age groups <60 years versus >60 years in PEX eyes
2. Pleomorphism and polymegathism for male and female PEX eyes versus non-PEX eyes.
3. Pleomorphism and polymegathism for glaucomatous versus non-glaucomatous PEX eyes.

A significant inverse relationship was found between endothelium and pleomorphism (p = .005) and a very strong inverse relationship was observed between endothelium and polymegathism (p < .00001) [Table 3].

DISCUSSION

This study has shown *in vivo* that the corneal endothelium is significantly affected quantitatively and qualitatively by cells producing pseudoexfoliation material. Similar changes have been reported by Miyake et al.[7] PEX eyes with glaucoma have more polymegathism than PEX eyes without glaucoma. The qualitative changes of the corneal endothelium by PEX, in the form of degenerating, irregular, loosely adherent cells have also been reported by Schlotzer et al.[8] Seitz and Naumann have reported 85% polymegathism in PEX endothelial cells compared to 98.4% in our study.[9] In another series, the same authors have reported 77% pleomorphism compared to our data of 96.8%. The difference could be due to more severe PEX in our patients. This study, however, revealed more pleomorphic values for PEX eyes with glaucoma than PEX eyes without glaucoma.

In contrast to their data, this study shows normal age-matched cell counts in most of the PEX eyes. Most of the recent series from different countries show a female preponderance of PEX; however, reports from Ethiopia,[10] Greece[11] and Oman[4] show that males are affected more than females. Notwithstanding, these data may be biased since the diagnoses have mainly been done on clinical grounds. Our study has revealed PEX glaucoma in a younger age group which means that these patients should be followed up early in life.

The present study shows less endothelial cell counts in the PEX eyes with glaucoma as compared to PEX eyes without glaucoma. The difference, however, is not significant. This observation is supported by Knorr et al.[12] Thus, even though endothelial cell counts may be normal in age-matched PEX eyes, the latter may exhibit significant morphological changes with respect to their size/area (polymegathism) and shape/hexagonality (pleomorphism). This could be the reason for PEX keratopathy with subsequent early and rapid corneal decompensation.[13] Since cataract is the most common anterior segment intraocular surgery performed world wide, the implications of PEX on corneal endothelial cells are quite demanding.[14,15]

The overall incidence of intra-operative complications in PEX eyes has been reported to be 4-7% depending on the preexisting pathology. The general clinical opinion is that in PEX eyes a prolonged corneal recovery after intraocular surgery is frequent. This study has shown that corneal endothelial cell anomalies may provide a morphological basis for this event. The data clearly emphasises the importance of preoperative confocal analysis of PEX corneas.

CONCLUSION

Pseudoexfoliation in Omani population is associated with increased corneal endothelial pleomorphism and polymegathism predisposing to early corneal decompensation after intraocular, mainly cataract, surgeries, even when the endothelial cell counts may be within normal limits.

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