Egyptian Journal of Medical Research (EJMR)

Effect of Glaucoma on Corneal Endothelium

Hazem Effat Abd El-Ghany Mohammad Haroon [1], Asmaa Mohamed Samir [1], Haytham Ibrahim Ibrahim El-Shawaf [2], Muller Victor Shaker [1]

Ophthalmology Department, [1] Faculty of Medicine, Beni-Suef University, [2] Research Institute of Ophthalmolgy, Egypt

Abstract:

Background: Glaucoma is a group of diseases characterized by a specific pattern of optic nerve neuropathy and retinopathy which is permenant. There is increasing evidence of glaucoma-associated corneal endothelial changes. Decrease ECD has been reported in various types of glaucoma such as primary angle-closure glaucoma, primary open-angle glaucoma (POAG) and some types of secondary glaucoma. **Objectives:** The purpose of this study is to evaluate the status of corneal endothelium in different type of open angle glaucoma patients by using Specular microscope comparing with the normal ones. **Patients and Methods:** We included (120) subjects in this study of normal and open angle glaucoma patients. This present study was a case control study; conducted on 60 open angel glaucoma patients (22 male, 38 female) with age ranged from (28) to (60) and an average 53.56 ±7.6years, compared with 60 healthy control individuals matched in age and sex. **Results:** There is positive relationship between ECD and glaucoma which is significant in open angle than normal population. This may be of value during our daily clinic practice especially when dealing with refractive surgery and glaucoma suspects. Quantitative analysis of CEC morphology of glaucoma patient is necessary by specular microscopy. We should measure CCT and consequently we can adjust IOP to judge the real IOP of the patient and take a good reasonable decision in the treatment of glaucoma patients. High IOP should be controlled as soon as possible to prevent optic neuropathy and corneal endothelial damage. **Conclusion:** Glaucoma and its management may have deleterious effects on the corneal endothelium. There is still much more to learn about how increased IOP, mechanical forces, and the aqueous environment contribute to corneal endothelial cell loss broadly observed in the milieu of glaucoma treatment. A history of glaucoma surgery poses a particularly significant risk to corneal endothelial cell health and cornea transplant graft survival.

Keywords: Glaucoma, Corneal Endothelium.

1. Introduction:

The corneal endothelium is critical in maintaining a healthy and clear cornea. Corneal endothelial cells have a significant reserve function, but preservation of these cells is paramount, as they have limited regenerative capacity. The corneal endothelium is the innermost layer of the human cornea and despite being just a single layer of cells, fulfills a key function in preserving transparency by maintaining the cornea in a state of relative dehydration. The endothelium achieves this by a mechanism known as the pump-and-leak hypothesis [1].

An incomplete belt of tight junctions between the endothelial cells allows passive diffusion fluid from the anterior chamber to “leak” through and supply the corneal stroma with nutrients. If this were to continue unabated, however, the excessive passage of fluid through the barrier would swell the cornea and reduce transparency. To counteract the leaking, endothelial cells actively “pump” in the opposite direction. These cells possess Na+/K+ pumps that create local osmotic gradients and actively draw fluid back into the anterior chamber, reaching a state of equilibrium and corneal transparency (Figure1) [2]. Thus damage to the corneal endothelium is irreversible. Loss of CECs occurs as a consequence of intraocular surgery, trauma or diseases such as diabetes and glaucoma [3]. At the early stage of endothelial damage, neighboring cells spread and/or migrate to compensate for the cell loss, which results in an increase in cell size and/or alteration of cell shape. Progression of cell loss further compromises corneal transparency and causes corneal edema, bullous keratopathy and impaired visual acuity [4].

Glaucoma is a group of diseases characterized by a specific pattern of optic nerve neuropathy and retinopathy which is permenant. The most common type is open-angle glaucoma with less common types including closed-angle glaucoma and normal-tension glaucoma. Open-angle glaucoma develops slowly over time and there is no pain. Peripheral vision may begin to decrease followed by central vision resulting in blindness if not treated [5].

There is increasing evidence of glaucoma-associated corneal endothelial changes. Loss of CECs has been reported in various types of glaucoma such as primary angle-closure glaucoma, primary open-angle glaucoma (POAG) and some types of

secondary glaucoma [5]. Endothelial cell loss is attributed to both glaucoma itself and treatment that lowers intraocular pressure (IOP). A direct compression mechanism due to elevated IOP has been proposed in CEC loss in acute angle-closure glaucoma [6]. Glaucoma surgery has been reported in patients after application of antiproliferative medications in filtration surgery and aqueous shunt implantation [7].

In this study, we aimed to document the corneal endothelial changes in patients with open angle glaucoma by comparing their specular endothelial microscopy results with normal age matched people.

Aim Of The Work:

The purpose of this study is to evaluate the status of corneal endothelium in different type of open angle glaucoma patients by using Specular microscope comparing with the normal ones.

2. Patients And Methods:

Type of study: A prospective case control study.

Study period: This study was conducted in the period from February 2019 till August 2019.

Study population: Normal and glaucomatous patients attending to Research Institute of Ophthalmolgy**.**

Sample size: A total 120 cases from General Ophthalmic Clinic and Glaucoma Outpatient Clinic at Research Institute of Ophthalmolgy. These cases subdivided into 2 groups; 60 normal cases and 60 glaucomatous patients coming for follow up according to:

Inclusion criteria:

- Age of patients: from 20 years to 60 years.
- Gender: both type of gender.
- Different types of open angle glaucoma.
- Best corrected visual acuity 20/200 or better.
- A healthy anterior segment appearance on examination with slit-lamp biomicroscopy; clear cornea, open angles gonioscopy G3,G4; and reliable visual field (VF) results.

Exclusion criteria

- A history of corneal disease, inflammation, trauma, contact lens wearer or history of ocular surgery (except for uncomplicated cataract surgery).
- Other diseases affecting the specular microscopy (e.g. Corneal pathology, trauma….).

3. Methods:

- **Study Procedures:** All patients were subjected to:
  - Visual acuity assessment using Auto Refractometer, refraction and best corrected visual acuity (B.C.V.A) assessment using Snellen chart.
  - Slit lamp examination of anterior chamber.
  - Gonioscopy
  - Fundus examination using slit lamp biomicroscopy with +90 Diopter lens.
  - Intraocular pressure measurement by Applanation Tonometer.
  - Specular microscopy (Non-contact Nidek-CEM 530)

Statistical Analysis:

Data were analyzed using SPSS version 22; bivariate analysis will be done using suitable statistical tests; results will be considered significant for p-values less than 0.05. Data were coded and entered using the statistical package SPSS version 23. Data was summarized using mean and standard deviation for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. P-values <less than 0.05 were considered as statistically significant**.**

4. Results:

Table 2: Basic characteristics of the studied open angle glaucoma patients and control group:

	Descriptive statistics of OAG	**Descriptive statistics of control group**
Age; (years)		
Mean ±SD	53.56 ±7.6	52.75±5.4
Range (minimum-maximum)	32 (28-60)	33 (27-60)
Gender; N (%)		
Male	22 (38.7%)	21 (35%)
Female	38 (61.3%)	39 (65%)
Medical History; N (%)		
DM	7 (11.29%)	6 (10%)
HTN	12 (19.35%)	10 (16.66%)
Ophthalmic history; N (%)		
RT PHAC0	8 (12.9%)	5 (8.33%)

LF PHACO	7 (11.29%)	4 (6.66%)
LF ECCE	2 (3.22%)	

Table 3: Ophthalmic Examination of the studied primary open angle glaucoma eyes and control group:

	Descriptive statistics of OAG	**Descriptive statistics of control group**
Visual acuity		
Mean ±SD	0.45 ±0.2	0.6±0.2
Range (minimum-maximum)	0.90 (0.10 – 1)	0.40 (0.6 – 1)
Gonioscopy grading		
G3	51 (58.6%)	
G4	22 (25.3%)	19 (31.66%)
G3,G4	14 (16.1%)	41 (68.33%)
IOP		
Mean ±SD	16.78 ±2.6	14.25±2
Range (minimum-maximum)	14 (8 – 22)	6 (10– 16)

Table 4: Endothelial cell characteristics of healthy eyes and OAG eyes

	OAG Eyes (N= 87)	**Healthy Eyes (N= 62)**	***p-value***
NUM	107.95 ±49.06	146.95 ±41.41	<0.001*
CD, cells/mm²	2427.78 ±515.02	2582.85 ±355.39	0.042*
AVE, µm²	444.05 ±145.66	395.80 ±65.12	0.016*
SD, µm²	119.58 ±53.82	105.27 ±21.18	0.026*
CV, %	0.28 ±0.07	0.28 ±0.03	0.808
MAX, µm²	1069.00 ±324.96	928.67 ±222.28	0.007*
MIN, µm²	185.35 ±134.47	144.77 ±18.65	0.020*
HEX, %	0.68 ±0.08	0.68 ±0.04	0.564
CCT	550.68 ±36.08	536.17 ±66.65	0.089

p-value ≤ 0.05 is considered significant by Independent Sample t-test.

OAG: open-angle glaucoma; NUM: CD: Cell density; AVE: Average cell area; SD: Standard deviation; CV: Coefficient of variation; MAX: Maximum cell area; MIN: Minimum cell area; HEX: Percentage of hexagonal cells; CCT: central corneal thickness.

NUM was significantly lower in eyes with OAG compared with normal control eyes; (107.95 ±49.06 vs. 146.95 ±41.41) in OAG and controls respectively. Cell density (CD) was significantly lower in patients with OAG (2427.78 ±515.02 cells/mm2) compared to the control group (2582.85 ±355.39 cells/mm2). The average cell area was significantly increased in glaucoma eyes (444.05 ±145.66 µm2) compared with the control group (395.80 ±65.12 µm2). Consistently, glaucoma patients exhibited statistically significant increased maximum, minimum and SD of cell area. There were no significant differences in the coefficient of variation of cell area (CV %), percentage of hexagonal cells (HEX %) and central corneal thickness (CCT) between the two groups.

Table 5: Correlations between endothelial cell characteristics and IOP among studied glaucoma eyes:

	IOP	
	r	**p-value**
NUM	0.063	0.561
CD, cells/mm²	-0.299	**0.005***
AVE, µm²	0.235	**0.029***
SD, µm²	0.031	0.777
CV, %	-0.059	0.585
MAX, µm²	0.286	**0.007***
MIN, µm²	0.284	**0.008***
HEX, %	0.089	0.411
CCT	0.111	0.308

p-value ≤ 0.05 is considered significant.

r= Spearman's rank correlation coefficient

NUM: CD: Cell density; AVE: Average cell area; SD: Standard deviation; CV: Coefficient of variation; MAX: Maximum cell area; MIN: Minimum cell area; HEX: Percentage of hexagonal cells; CCT: central corneal thickness.

The coefficient of variation of cell area (CV %), percentage of hexagonal cells (HEX %) and central corneal thickness (CCT) were not correlated with IOP in the studied OAG eyes.

5. Discussion:

In our study, 60 case(87 eyes) chronic primary open angle glaucoma which are controlled on medical treatment only without any history of glaucoma surgery. Average age of patients in our study are 53.56 ±7.6years, compared with 60 healthy control individuals matched in age and sex. Several studies have revealed that patients with glaucoma may have lower corneal endothelial cell density than those without glaucoma of the same age group.

In July 1990, China, study includes 87 cases of unilateral glaucoma were studied with the TOCEB-160 IV specular photomicroscope, and the healthy fellow eyes served as controls. The endothelial cell density was found decreased in majority of the morbid eyes by an average 12.7% in acute angle-closure glaucoma (34 cases), by 5.34% in chronic angle-closure glaucoma (23 cases), and by 12.4% in glaucoma cyclitis syndrome (30 cases). The average diminution of endothelial cell densities after filtering operations in 16 eyes was 10.2%, and after Nd:YAG laser iridotomy it was 5.11%. The authors are of the opinion that estimation of endothelial cells before operations and precautions against endothelial damage during operations invading the anterior chamber are necessary, especially for cases with risk factors such as trauma, uveitis, persistent high IOP, old age, or history of intra-ocular surgery [8].

In March 1991, German, in 3204 normal eyes with normal intraocular pressure (10-20 mmHg), the cell count was observed to be age-dependent and to have an average value of 2293 ± 394 cells/mm2; the cells generally had a regular arrangement. In 302 eyes with primary, chronic, open-angle glaucoma with intraocular pressures between 19 and 32 mmHg, there was a significant (p less than 0.001) reduction, in cell count to 1582 ± 248 cells/mm2. The cell picture was composed of clearly enlarged, but regularly arranged cells. A statistical evaluation (matched age groups, etc.) was carried out using the Mann-Wilcoxon rank test and using standard specular microscopic examinations (Bio Optics LSM 2000 and Clinical Specular Microscope Camera) to evaluate the endothelial cell count [9].

In May 1997, Canada, study includes One hundred two patients with glaucoma were compared with 52 patients without glaucoma of the same age group revealed that Corneal endothelial cell counts were significantly lower in patients with glaucoma (2,154 ± 419 cells/mm2) than in controls (2,560 ± 360 cells/mm2; t test, $p < 0.0001$). In the glaucoma group, cell counts were inversely proportional to the means of IOPs. Patients receiving three or four

glaucoma medications had lower cell counts than those receiving one or two medications. Cell counts were significantly lower both in primary angle-closure glaucoma and in primary open-angle glaucoma [10].

In 2005, Poland, study include 159 patients (233 eyes) with glaucoma and 37 patients (44 eyes) with pseudoexfoliation syndrome were analyzed using the Noncon Robo (Konan) non-contact specular microscope. Patients, 22-91 years old, were divided into 8 groups according to the clinical diagnosis and for each group an adequate control group was matched that revealed that Corneal endothelial cell density were significantly lower in all groups of glaucoma patients. There was a significant reduction in cell count in patients with chronic angle-closure glaucoma: 2333 ± 476/mm2, control group (C): 2809 ± 378/mm2, p< 0.001), acute angle-closure glaucoma 2136 ± 620/mm2, C. 2780 ± 384/mm2, p< 0.001, pigmentary glaucoma 2537 ± 355/mm2, C. 3003 ± 335/mm2, p< 0.05, juvenile glaucoma 2337 ± 277/mm2, C. 3001 ± 168/mm2, p< 0.001, primary open angle glaucoma 2326 ± 231/mm2, C. 2779 ± 398/mm2, p< 0.001, normal tension glaucoma 2343 ± 394/mm2, C. 2732 ± 356/mm2, p< 0.01, capsular glaucoma 2128 ± 483/mm2, C. 2753 ± 354/mm2, p< 0.001 and in patients with pseudoexfoliation syndrome 2255 ± 299/mm2, C. 2721 ± 352/mm2, p< 0.001 so Patients with glaucoma have lower mean corneal endothelial cell density than control groups. The density of corneal endothelial cells depends on the type of glaucoma [11].

In November 2009, Korea, study include a total of 227 subjects in three groups, one each of normal-tension glaucoma and primary open-angle glaucoma patients and one of normal controls which revealed that The mean endothelial cell densities in the three groups were as follows: normal-tension glaucoma group, 2696.7±303.9 cell/mm2; primary open-angle glaucoma group, 2370.5±392.3 cell/mm2; and normal group, 2723.6±300.6 cell/mm2. The endothelial cell count was not significantly different between normal-tension glaucoma and normal groups (P=1.000). Primary open-angle glaucoma patients had significantly lower endothelial cell counts (P<0.001) than the normal group. The endothelial cell count was also significantly lower in eyes with primary open-angle glaucoma than in normal-tension glaucoma eyes (P<0.001). None of the patients included in this study were using glaucoma medications, indicating that the differences observed most likely were attributable to the IOP differences [12].

In April 2010, Croatia, study included 50 patients suffering from glaucoma and 50

patients in control group, the galacomatous patients subdivided into in separate groups also 30 patients with open angle glaucoma, 12 patients with angle closure glaucoma and 8 patients with pseudoexfoliative glaucoma. Specular microscopy was performed on central corneas. We used Tomey-EM non contact specular microscope which revealed that corneal endothelial density was significantly lower in patients with glaucoma than in control group. In glaucoma group corneal endothelial cell counts were 2148+/317 cells/mm2. In control group results were 2528+/–306 cells/mm2 (t-test, p<0.0001).In glaucoma patients group, open angle glaucoma group-corneal endothelial cells counts were 2153+/–217 cells/mm2. In group of patients with angle closure glaucoma corneal cell density was 2113+/–243 cells/mm2, so there was no significant difference between these two groups. But, the group with pseudoexfoliative glaucoma showed signifficantly lower values 2024+/–254 cells/mm2 (t-test, p<0.0001), So in conclusion this study showed that patients with glaucoma have lower central corneal endothelial cell density than those without glaucoma of the same age group. Also, patients with pseudoexfoliative glaucoma had lower values of central endothelial cell density comparing to patients with open angle or angle closure glaucoma [13].

In April 2014, study includes three groups of eyes from age-matched patients: [Group 1] normal controls (n=41); [Group 2] glaucoma with medical management only (n=15); [Group 3] glaucoma with prior glaucoma surgery (trabeculectomy or tube shunt) ± concurrent medical management (n=11) using specular microscope Konan NSP-9900 which revealed that Glaucoma patients collectively had a significantly lower ECD (2407 cells/mm^2 ± 430, mean ± S.D.) than controls (2675 cells/mm^2 ± 210), (p=0.001). Mean ECD was significantly lower in eyes with prior glaucoma surgery (2280 cells/mm^2 ± 539) than controls (p<0.0005). Surgically treated eyes had lower mean ECD as compared to eyes with medically treated glaucoma (2500 cells/mm^2 ± 295), however this difference was not statistically significant (p=0.069). There was no significant difference in CV (p=0.974) or HEX (p=0.970) between the corneal endothelia of these three groups [14].

In August 2019, China, study performed on 60 eyes of 60 patients with POAG comparing to healthy controls of the same age group using Indirect specular microscopy (TOPCON SP-2000P) which revealed that Endothelial cell density was 2959 ± 236 cells/mm2 in healthy controls and 2757 ± 262 cells/mm2 in patients with POAG. The POAG eyes had significantly

lower endothelial cell density compared to healthy control eyes (P < 0.001). In the POAG group, endothelial cell density was 2686 ± 233 cells/mm2 in the patients receiving medication and 2856 ± 272 cells/mm2 in the untreated subgroup. The eyes receiving medication had significantly lower endothelial cell density compared to untreated eyes. There was a negative correlation between cell density and mean IOP (r = -0.286, P = 0.004), positive correlation between the average cell area and mean IOP (r = 0.228, P = 0.022), maximum cell area and mean IOP (r = 0.218, P = 0.029) and minimum cell area and mean IOP (r = 0.290, P = 0.003). The percentage of hexagonal cells was not correlated with mean IOP. So in conclusion patients with POAG have lower corneal endothelial cell density than healthy controls of the same age [15].

Our study results concide with the previous studies in which Open angle glaucoma affects on the endothelial cell count.

The mechanisms leading to lower cell counts in patients with glaucoma are unknown. Gagnon et al. formulated three hypotheses: damage from direct compression of the corneal endothelium because of higher IOP; congenital alteration of both the corneal endothelial cell layer and the trabecular meshwork in patients with glaucoma; and glaucoma medication toxicity [10].

On the other hand, there are studies which find that no correlation between endothaelial cell count, IOP and open angle glaucoma as a disease

Some researchers hypothesized that CEC changes are not associated with high IOP [16].

In China, in August 2000, Study includes 125 eyes of 68 patients with glaucoma were compared with 63 eyes of 32 patients without glaucoma in the same age group which revealed that corneal endothelium density was significantly lower in patients with glaucoma[(2386.81 ± 289.76)/mm2] than that in controls [(2540.78 ± 195.66)/mm2]. Cell density of primary angle-closure glaucoma(PACG) [(2262.65 ± 338.64)/mm2] was significantly low, especially in acute PACG[(1925.16 ± 403.38)/mm2]. The area of endothelium became bigger than normal. But the endothelium density and morphology of primary open-angle glaucoma(POAG) and non-acute PACG had no changes. No correlation was found between mean recent IOP and endothelium density [17].

Another study on glaucoma medications do cause changes in corneal endothelial cells. Dilutions of 1/100, 1/1,000, and 1/10,000 of betaxolol, timolol,

levobunolol, carteolol, dipivefrin, dorzolamide, brinzolamide, latanoprost, unoprostone, and pilocarpine have all increased intracellular calcium in bovine corneal endothelial cells, whereas brimonidine decreased intracellular calcium concentrations. These deviations in calcium mobility may alter endothelial function, as calcium mediates endothelial cell apical junctions, paracellular calcium permeability, and subsequent corneal swelling [18].

A follow-up the study by Wu and colleagues found among the same medications that 1/100 dilutions of betaxolol, brimonidine, dorzolamide, dipivefrin, latanoprost, and unoprostone caused the release of lactate dehydrogenase, a marker of cell lysis. Other medications assayed in that study, including dilutions of the preservative benzalkonium chloride, did not affect lactate dehydrogenase release [19].

Dorzolamide lowers IOP by inhibiting carbonic anhydrase isozyme II, which is present not only in the aqueous producing ciliary body, but also in corneal endothelial cells.In studies of dorzolamide, no difference in ECD loss or corneal thickness was observed in comparison to topical beta blocker drops. A 1-year randomized controlled trial of topical dorzolamide, timolol, or betaxolol drops in patients with normal corneas showed ECD loss of 3.6%, 4.5%, and 4.2%, respectively, which were not found to be statistically different. There was no control group in this study for comparison. Theoretically, carbonic anhydrase inhibitors such as dorzolamide may affect pump function due to the presence of carbonic anhydrase isozyme II in these cells, but the authors suggest that the functional reserve of the endothelial cells prevents a clinically significant effect [20].

Since this study included only normal corneas, these findings cannot be generalized to patients with low ECD (300:500 cells/mm2), as this inhibition may be more clinically significant due to decreased functional reserve. Another 1-year randomized controlled trial of latanoprost, latanoprost-timolol, or timolol also did not find any differences from baseline endothelial measurements or among treatment groups [21].

Another study of normal corneas found no difference in the ECD, percent hexagonal cells, or coefficient of cell variation of cell area in patients treated with latanoprost versus latanoprost and brinzolamide, another carbonic anhydrase inhibitor [22].

In longer follow-up studies, the results were similar. Baratz and colleagues studied glaucoma patients enrolled in a 6-year ocular hypertension treatment study group that underwent yearly specular

microscopy. In that study, no differences were detected in ECD, percent hexagonal cells, or coefficient of cell variation of cell area between patients using topical glaucoma medications and untreated controls. The0.68% per year rate of endothelial cell loss in the medically treated group was similar to the 0.6% yearly loss reported in normal corneas [23].

6. Conclusion:

Glaucoma and its management may have deleterious effects on the corneal endothelium. There is still much more to learn about how increased IOP, mechanical forces, and the aqueous environment contribute to corneal endothelial cell loss broadly observed in the milieu of glaucoma treatment. A history of glaucoma surgery poses a particularly significant risk to corneal endothelial cell health and cornea transplant graft survival. Targeted approaches investigating the effect of protein-mediated changes in the aqueous on corneal endothelial cells and the surrounding environment are promising avenues to pursue a deeper understanding of glaucoma associated endothelial cell damage.

As discussed in this review, many studies are limited by short follow-up periods, inability to isolate a single variable, and variation in medical and surgical treatment of glaucoma. Although research design is beyond the scope of this discussion, high-quality studies utilizing control groups and support from in vitro models that manipulate single variables will be important in developing a greater understanding of corneal endothelial cell damage in glaucoma. Understanding these mechanisms is vital to the prevention of corneal decompensation, prevention of graft failure and subsequent repeat surgeries, and maintenance of clear vision.

7. References:

1. Barry PA, Petroll WM, Andrews PM, Cavanagh HD, Jester JV. The spatial organization of corneal endothelial cytoskeletal proteins and their relationship to the apical junctional complex. Invest Ophthalmol Vis Sci, 1995; 36 (6): 1115-1124.
2. Bourne WM. Biology of the corneal endothelium in health and disease. Eye (Lond), 2003; 17(8): pp: 912-918.
3. Urban B, Bakunowicz-Łazarczyk A, Michalczuk M, Krętowska M. Evaluation of corneal endothelium in adolescents with juvenile glaucoma. J Ophthalmol 2015; 2015: 895428.

4. Aldrich BT, Schlötzer-Schrehardt U, Skeie JM, Burckart KA, Schmidt GA, Reed CR, Zimmerman MB, Kruse FE, Greiner MA. Mitochondrial and Morphologic Alterations in Native Human Corneal Endothelial Cells Associated With Diabetes Mellitus. Invest Ophthalmol Vis Sci 2017; 58: 2130-2138.

5. Kusakabe A, Okumura N, Wakimasu K. Effect of trabeculotomy on corneal endothelial cell loss in cases of postpenetrating-keratoplasty glaucoma. Cornea. 2017;36:317-21.

6. Chen MJ, Liu CJ, Cheng CY, Lee SM. Corneal status in primary angle-closure glaucoma with a history of acute attack. J Glaucoma. 2012; 21:12-6.

7. Ates H, Palamar M, Yagci goldA, Egrilmez S. Trabeculectomy Versus EX-PRESS Shunt Versus Ahmed Valve Implant: Short-term Effects on Corneal Endothelial Cells. Am J Ophthalmol 2016; 162: 201-202.

8. Zhou WB. Zhongshan Ophthalmic Center, Sun Yat-sen University of Medical Sciences, Guangdong Province, 1991.

9. Knorr HL, Jünemann A, Händel A, Naumann GO. Morphometric and qualitative changes in corneal endothelium in pseudoexfoliation syndrome. Fortschritte der Ophthalmologie: Zeitschrift der Deutschen Ophthalmologischen Gesellschaft. 1991; 88(6):786.

10. Gagnon MM, Boisjoly HM, Brunette I. Corneal endothelial cell density in glaucoma. Cornea. 1997; 16:314-8.

11. Zarnowski T1, Lekawa A, Dyduch A, Turek R, Zagórski Z. Z Katedry i I Kliniki Okulistyki im. prof. Tadeusza Krwawicza Akademii Medycznej im. Feliksa Skubiszewskiego w Lublinie, 2005

12. Cho SW, Kim JM, Choi CY, Park KH. Department of Ophthalmology, Sungkyunkwan University School of Medicine, Kangbuk Samsung Hospital, Seoul, Korea, 2009.

13. Novak-Stroligo M, Alpeza-Dunato Z, Kovacević D, Caljkusić-Mance T. Department of Ophthalmology, Rijeka University Hospital, Rijeka, Croatia. Majanovakstroligo @gmail.com, 2010.

14. Mark PB, Jianyan H, Cristina M, Srinivas RS, Vikas C, Olivia LL. April 2014.

15. Yu ZY, Wu L, Qu B. Department of Ophthalmology, 4 Affiliated Hospital of China Medical University, Eye hospital of China Medical University, Key Laboratory of Lens Research of Liaoning Province, Shenyang 110005, Liaoning Province, China, 2019.

16. Verma S, Nongpiur ME, Husain R, Wong TT, Boey PY, Quek D, Perera SA, Aung T. Characteristics of the Corneal Endothelium Across the Primary Angle Closure Disease Spectrum. Invest Ophthalmol Vis Sci. 2018;59:4525-4530.

17. Luo Y, Li J, Jin Y. Department of Ophthalmology, PUMC Hospital, CAMS, PUMC, Beijing 100730, China. luo.yan@263.netknorr, 2000.

18. Wu KY, Hong SJ, Wang HZ. Effects of antiglaucoma drugs on calcium mobility in cultured corneal endothelial cells. Kaohsiung J Med Sci. 2006; 22:60-7.

19. Wu KY, Wang HZ, Hong SJ. Cellular cytotoxicity of antiglaucoma drugs in cultured corneal endothelial cells. Kaohsiung J Med Sci. 2007;23:105-11.

20. Lass JH, Khosrof SA, Laurence JK. A double-masked, randomized, 1-year study comparing the corneal effects of dorzolamide, timolol, and betaxolol. Dorzolamide Corneal Effects Study Group. Arch Ophthalmol. 1998; 116:1003-10.

21. Lass JH, Eriksson GL, Osterling L, Simpson CV. Comparison of the corneal effects of latanoprost, fixed combination latanoprost-timolol, and timolol: a double-masked, randomized, one-year study. Ophthalmology. 2001; 108:264-71

22. Nakano T, Inoue R, Kimura T. Effects of brinzolamide, a topical carbonic anhydrase inhibitor, on corneal endothelial cells. Adv Ther. 2016;33:1452-9.

23. Baratz KH, Nau CB, Winter EJ. Effects of glaucoma medications on corneal endothelium, keratocytes, and subbasal nerves among participants in the ocular hypertension treatment study. Cornea. 2006; 25:1046-52.