Corneal Endothelial Status in Patients with Primary Open Angle Glaucoma and Normal Tension Glaucoma - A Comparative Study

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ABSTRACT

BACKGROUND

Corneal endothelial cells are one of the major factors responsible for maintaining corneal transparency. Since they cannot regenerate, the factors which affect them adversely should be looked into. Heredity, increasing age, topical drug use, high intraocular pressures etc., are some of them. Corneal endothelial cells are badly affected in acute and chronic angle closure if the pressures remain high for longer periods. So, we wanted to know whether mild to moderate increase in IOP as in Primary Open Angle Glaucoma (POAG) will affect the corneal endothelial status. If high intra ocular pressure is the sole factor, then the endothelial cells should be normal in Normal Tension Glaucoma (NTG). Hence, a study was undertaken to compare the corneal endothelial status of POAG and NTG. We wanted to study and compare corneal endothelial status in patients with primary open angle and normal tension glaucoma.

METHODS

The study was conducted in the Glaucoma clinic in a tertiary care hospital in Northern Kerala. It was a facility based comparative cross sectional study. 142 glaucoma patients were included in the study. They were divided into Primary Open Angle Glaucoma (POAG) and Normal Tension Glaucoma (NTG) groups. Endothelial status was studied using specular microscope. Relevant clinical examination, central corneal thickness, IOP measurement and field analysis by HFA was done in all patients.

RESULTS

Mean age was 54.7 ± 5 years in POAG and 54.65 ± 6.2 years in NTG. Females were more affected by the disease in both groups. Age showed a statistically significant association with endothelial cell density. As age increases by one-year, endothelial cell density decreases by 5.078 cell / mm^2. POAG group had endothelial cell density 160 cell/ mm^2 lower than NTG (p value 0.000). Average hexagonality is 3.73 lesser in POAG than NTG (p value 0.005).

CONCLUSIONS

High intraocular pressure or wide fluctuations can contribute to endothelial cell damage as well as progression of glaucoma. This indicates the importance of achieving target IOP and maintaining it in the treatment of POAG as well as NTG. Anti-glaucoma medications should be selected cautiously in patients with compromised endothelium. Surgical procedures should be done with adequate precautions in glaucoma patients with reduced endothelial count.

KEYWORDS

Corneal Endothelium, Primary Open Angle Glaucoma, Normal Tension Glaucoma, and Corneal Decompensation.

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BACKGROUND

Corneal endothelium plays an important role in regulating stromal hydration and maintaining transparency. The two main functions of corneal endothelial cells are barrier function, which is mediated by zonula occludens - 1, and pump function, which is due to an active (Na^+/K^+-ATPase) pump[1] Endothelium is a single layer of squamous cells, hexagonal in shape and non-replicating. Endothelial cell density (ECD) at birth is approximately 4000-5000 cells/ mm and decreases with age.[2] The cell density decreases at a larger rate during the first two years, probably due to increase in corneal diameter. Once adult size is reached there is a slower decline in cell density. For maintaining the barrier and pump function the critical cell density is 400-500 cells / mm[3, 3] The number of endothelial cells in healthy eyes decreases at the rate of 0.3 % per year.[4] In healthy cornea around 75% of endothelial cells are hexagonal.[3] Endothelial dystrophy[5] intraocular surgery[5] trauma,[6] drugs,[6] systemic diseases like diabetes[5] and chronic renal failure[6] can cause decrease in the endothelial cell count. This in turn affects the barrier function of the endothelium and increases the risk of developing post-operative corneal edema. The main factor leading to endothelial cell loss is believed to be raised intraocular pressure. Patients with glaucoma have lower endothelial cell count when compared to normal individuals.[5] There are studies showing that even Normal tension glaucoma patients have lower endothelial cell density than normal controls.[5-7] The reason for the lower endothelial cell density in eyes with NTG is not known. In this study we aimed to find out the correlation between IOP and endothelial cell count by comparing the changes in corneal endothelial cell density in eyes with NTG and POAG.

METHODS

In this comparative cross-sectional study, 142 glaucoma patients were divided into POAG and NTG groups. The study period was one year, and the sampling method was convenient consecutive sampling. The study was conducted in the glaucoma clinic in the Department of Ophthalmology Government Medical College Kozhikode.

A written informed consent was obtained from all patients taking part in the study, after approval from institutional ethics committee. All patients underwent a detailed evaluation which included visual acuity using Snellen chart, slit lamp bio microscopy, gonioscopy, applanation tonometry and field analysis by HFA (Zeiss SR No: 7208371) RNFL analysis by OCT (Spectral OCT SLO SN 1461). Specular microscopy (SP 3000P) was performed to study the corneal endothelium. An average of 3 readings of the endothelial counts in the central quadrants were taken. 100 cells were counted with the variable frame analysis by center cell counting method in both groups. Each eye was considered separately during analysis. Each patient was examined and data collected personally to ensure quality. There was no missing values.

Exclusion Criteria

Patients with previous history of ocular surgery, blunt or penetrating trauma, ocular inflammation, contact lens wear, corneal dystrophy, primary angle closure and secondary glaucoma.

Statistical Analysis

Statistical analysis was done using SPSS 14 software (Chicago, IL, United States). Chi square test and one-way ANOVA test was done to find significance of difference. t test was used to find significant difference between groups. Regression was performed using multiple linear regression. P value less than 0.05 was considered significant.

RESULTS

Corneal endothelial cells decrease with age in both POAG and NTG and was statistically significant.

		POAG			NTG		
	Age	N	Mean ± SD	P Value	N	Mean ± SD	P Value (ANOVA)
Density RE	< 50 yrs.	27	2295.63 ± 112	0.021	9	2437.67 ± 180.57	0.145
	50 – 60 yrs.	44	2231.90 ± 95.56		23	2364.17 ± 162.75	
	> 60 yrs.	13	2222.77 ± 84.92		7	2270.71 ± 143.96	
Density LE	< 50 yrs.	26	2229.73 ± 126.05	0.024	9	2442.44.± 205.61	0.330
	50-60 yrs.	47	2261.21 ± 148.05		24	2411.33 ± 166.67	
	>60 Yrs.	15	2157.93 ± 99.50		9	2326.66 ± 154.05	

Table 1. Corneal Endothelial Cells Decrease with Age in POAG and NTG (ANOVA)

The mean endothelial cell density in right eye was 2250.98 ± 103.3 and in left eye 2234.3 ± 138.5 in the POAG group. In the NTG group mean endothelial cell density in RE was 2364.36 ± 168.4 and in LE was 2399.8 ± 1353 which was more when compared to the POAG group and was statistically significant (p- Value <.001). Hexagonality did not show any statistically significant difference between the two groups. Mean CCT was lower in the POAG group (RE - 495.72 ± 14.7 and in LE 490.72 ± 15.8)when compared to NTG group (RE - 507.74 ± 8.30 and LE - 509.37 ± 7.72) this was statistically significant with a p value of <.001(t test t value -5.001 and -5.284 in RE and LE respectively).Mean IOP was lower in the NTG group (RE - 14.72 ± 2.1, LE- 15.28 ± 1.98)as expected than the POAG group (RE - 18.14 ± 3.92, LE – 18.19 ± 2.9) which was also statistically significant with a p value of < .001 (t test t value 5.396 and 5.991 in RE and LE respectively)

Both groups showed statistically negative correlation of cell density with age. Hexagonality showed a statistically significant weak positive correlation with endothelial cell density in POAG group only. CCT and IOP did not have a significant correlation with endothelial cell density in this study.

	POAG		NTG	
	Density RE Pearson Co-efficient (p value)	Density LE Pearson co-efficient (p value)	Density RE Pearson co-efficient (p value)	Density LE Pearson co-efficient (p value)
Age	-0.309 (0.004)	-0.199 (0.043)	-0.468 (0.003)	-0.376 (0.014)
CCT	0.005 (0.964)	0.076 (0.480)	0.051 (0.756)	0.030 (0.551)
Hexagonality	0.222 (0.043)	0.261 (0.014)	0.212 (0.195)	0.217 (0.167)
IOP	0.009 (0.937)	-0.201 (0.202)	0.181 (0.270)	-0.201 (0.202)

Table 2. Correlation of Age, Central Corneal Thickness (CCT), Hexagonality and Intraocular Pressure (IOP) with Endothelial Cell Density in POAG and NTG Patients

Variable	Beta Co-efficient	p Value
Age	- 5.078	0.002
Groups (POAG/ NTG)	160.901	<.001
Average CCT	- 0.098	0.902
Average Hexagonality	3.713	0.005

Table 3. Multiple Linear Regression Showing the Association between Age, Type of Glaucoma, Average Central Corneal Thickness and Average Hexagonality with Corneal Endothelial Cell Density

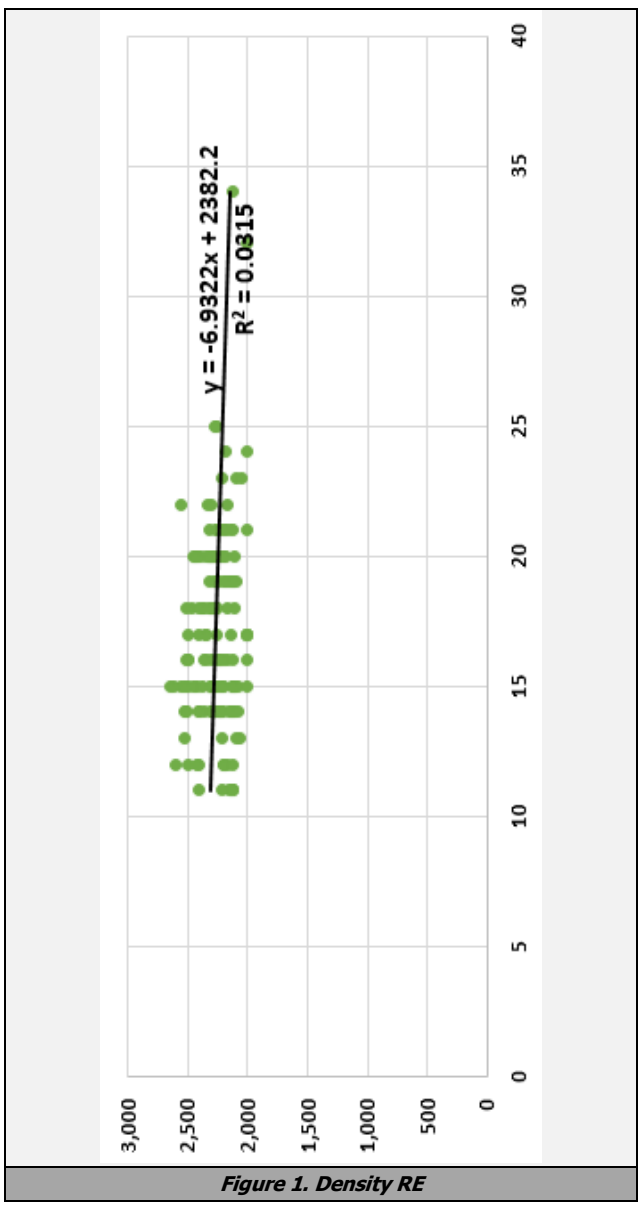

Figure 1. Density RE

Scatter diagram with regression equation for correlation analysis of corneal endothelial cell density with intraocular pressure in RE and LE. (Figure 3 & 4). Linear regression analysis was done between IOP variance and corneal endothelial cell density which showed an r^2 value of 0.031 in RE and 0.028 in LE which was statistically significant with a p value of 0.034 and 0.044 in RE and LE respectively

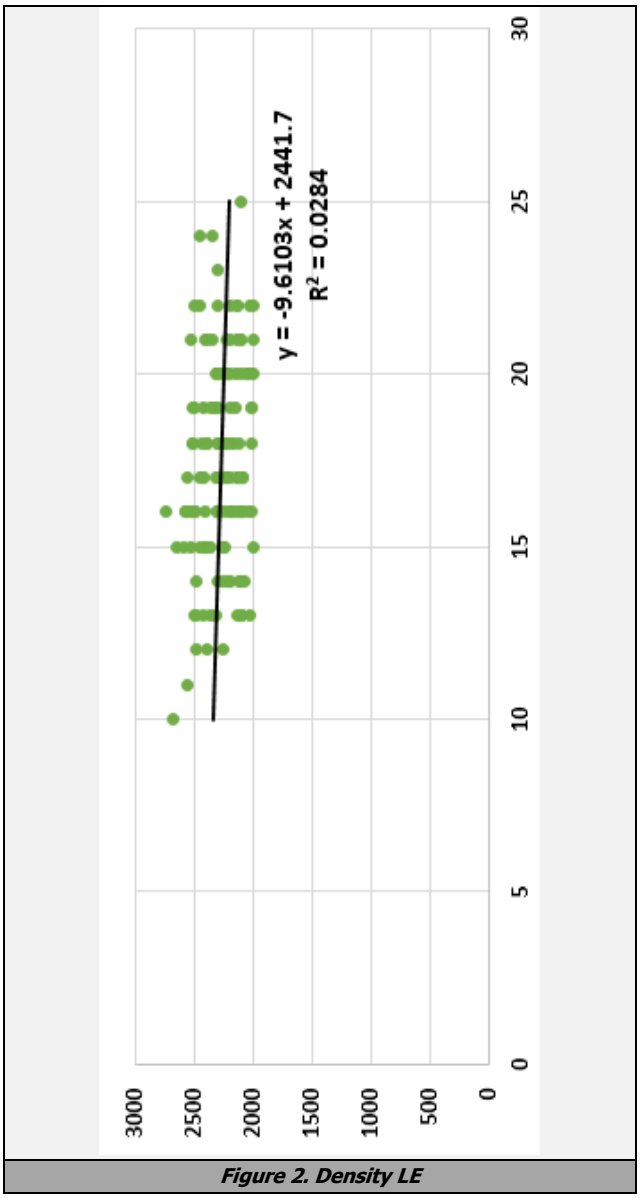

Figure 2. Density LE

Age showed a statistically significant association with endothelial cell density. As age increases by one year endothelial cell density decreases by 5.078 cell/ mm^2. POAG group had endothelial cell density 160 cell/ mm^2 lower than NTG (p value 0.000). Hexagonality showed an independent contribution with endothelial cell density. Average hexagonality is 3.713 lesser in POAG than NTG (p value 0.005).

DISCUSSION

One hundred and forty two glaucoma patients included in the study were divided into two groups. Ninety-nine patients (69.7 %) had primary open angle glaucoma and forty-three patients (30.3%) had normal tension glaucoma. Mean age was 54.7 ± 5 yrs in POAG and 54.65 ± 6 yrs. in NTG. Majority were between 50 - 59 years in both groups. Females [65/ 99 POAG patients (65.7%) and 29/ 43 NTG patients (67.4%)]

outnumbered males in this study. In the Rotterdam study[8] females with early menopause was found to have a higher risk of developing open angle glaucoma. So this shows that female endogenous sex hormones could have a protective role against open-angle glaucoma. In the study by Drance et al[9] NTG occurred more in women than men. The Aravind Comprehensive Eye Survey[10] to find out glaucoma in a rural population of southern India showed less predilection for females to have open angle glaucoma, unlike this study.

Rao et al[11] noticed decrease in endothelial cells with age in normal Indian eyes. The reason for the endothelial cell loss is cellular apoptosis and increase in corneal diameter in normal individuals.[12] In the present study also there is a reduction in corneal endothelial count with age in both groups but statistically significant in POAG group only.

Mean cell density in POAG group in our study was 2250.98 ± 103.3 which is comparable to the values in the study by Zarnowski et al.[7] Cell density was found to be lower in POAG in both eyes when compared to NTG and was statistically significant (p value 0.000). In a study by Cho et al[12] there was a significant reduction in endothelial cell density in eyes with POAG but not in NTG which as seen in our study. Studies by Zarnowski et al[7] and Gagnon et al[5] reports that patients with glaucoma may have a lower endothelial count than those without of the same age group. The mechanisms leading to lower cell counts in patients with glaucoma are not clear. Gagnon et al[5] formulated three hypotheses: 1) damage from direct compression of endothelium due to higher intra ocular pressure. 2) congenital alteration of endothelium and trabecular meshwork in patients with glaucoma. 3) glaucoma medication toxicity.

Hexagonality did not show any statistically significant difference between the two groups. In a study by Cho et al[12] there was no change in the hexagonality between NTG and POAG patients. In our study there was no statistically significant correlation between intraocular pressure and endothelial cell count. Nguyen[13] in his study on the impact of increased intraocular pressure on long term corneal endothelial cell density after penetrating keratoplasty found that there was no correlation between IOP and corneal endothelial cell count. So they concluded that mild to moderate IOP rise will not affect endothelial cell. In a study on characteristics of the corneal endothelium across the primary angle closure disease spectrum by Sushma Verma et al[14] there was no correlation of IOP with endothelial cell count. The probable causes postulated by them were, the endothelial cells could withstand small rise in the intraocular pressure or the intraocular pressures in the study group were controlled with medications.

There are two proposed mechanisms for the damage of endothelial cells due to high IOP. One is the dysfunction of the active pump mechanism and another one is the structural damage to the endothelial cells. The longer the duration of high intraocular pressure, the more severe the destruction of endothelial cells. If high IOP is controlled endothelial cells can recover their structure and function. If the high IOP persists for a longer period then the healing capacity of endothelial cells will decrease.[15]

Even though the mean IOP in the glaucoma group was in the normal range in this study, the endothelial cell count was less when compared to those with normal tension glaucoma. The probable reason could be that small rise in IOP over a long period contributes to decrease in corneal endothelial cell density. IOP fluctuations can also affect the function of the corneal endothelium[16] Sihota et al[17] reported significantly higher IOP fluctuations in POAG patients than in normal controls. The reasons for not getting a significant correlation between IOP and endothelial cell count in our study could be that, 1) IOP in the office hours could be normal, and peak IOP may be missed. 2) The IOP is medically controlled in the study group. 3) There may be wide fluctuations in IOP. To know about IOP fluctuations we need to do phasing in all POAG patients.

Sihota et al[18] in her study found that endothelial cell count was significantly lower in patients that have had an attack of acute angle closure glaucoma which proves the role of high IOP in causing damage to endothelial cells. There was no correlation between CCT and endothelial count in our study. Similar results were observed in the study by Tananuvat et al, Ventura et al.[19,20] The explanation for such an observation is that in corneas which have moderate reduction in the number of otherwise healthy endothelial cells, the corneal thickness does not increase. A healthy endothelium is thus able to maintain corneal dehydration over a large range of endothelial cell counts.[19,20] The reduction observed in endothelial cell density (ECD) in our study was moderate in both groups (average 2243 in POAG 2382 in NTG). The average ECD in Indian eyes studied by Rao et al[11] was 2525 ± 337/ $mm^{2.}$ So our study group had an apparently healthy endothelium which may be the reason for not getting a correlation between CCT and corneal endothelial count.

Another cause for the loss of endothelial cells in POAG proposed by Gagnon[5] is the effect of various anti glaucoma medications. Ayaki et al[21] found out that topical antiglaucoma drops produced endothelial cell toxicity due to the presence of benzalkonium chloride.

Limitations

There were no normal controls in our study, hence no normative data for comparison. Both the POAG and NTG groups were on treatment with antiglaucoma medications and the effect of topical medications on the endothelial cell count and intra ocular pressure was not taken into consideration in our study.

CONCLUSIONS

Corneal endothelial cell density and hexagonality which are markers of healthy endothelium was reduced more in POAG compared to NTG. Elevated IOP or fluctuations may adversely affect the corneal endothelium in addition to hastening the disease progression in glaucoma. Phasing may be helpful in detecting fluctuations or high values of IOP in patients with compromised endothelium. This study also tries to emphasize that in all patients with glaucoma, even if they are well controlled, utmost care should be given during

any type of surgery, as there is a chance of endothelial decompensation. It is always better to do specular microscopy in all of them before surgery and to take precautionary measures to prevent corneal decompensation. Anti-glaucoma medications should be selected cautiously in patients with reduced endothelial count.

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