Measuring Loss of Corneal Endothelial Cell Density and Retinal Nerve Fiber Layer Thickness in Primary Open Angle Glaucoma.

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ABSTRACT

Background: Primary open angle glaucoma is an irreversible disease causing a reduction in corneal endothelium cells mainly responsible for corneal clarity along with nerve fiber layer loss.

Objective: To calculate loss of corneal endothelium density (CED) and retinal nerve fiber layer (RNFL) thickness in Primary open angle glaucoma (POAG).

Material and Methods: It was a prospective observational study conducted in Khyber Teaching Hospital from April 2015 to December 2019. A total of 112 patients were included in the study through consecutive non-probability sampling technique. Patients were diagnosed with open angle glaucoma on the basis of intra ocular pressure (IOP), optic disc changes, visual fields changes and Optical coherence tomography (OCT) findings. Corneal endothelium density and thickness of retinal nerve fiber layer was calculated on the basis of specular microscopy and OCT. These were compared with normal matched values.

Results: The POAG patients have average 17.12% CED and 34.73% RNFL thickness loss.

Conclusion: It is observed that Corneal endothelial cell count may be evaluated along with nerve fiber layer thickness in Primary open angle glaucoma.

Key words: Specular microscopy, OCT, RNFL, POAG.

This article may be cited as: Khan BS, Nawaz A, Ahmad I, Shah Z. Measuring Loss of Corneal Endothelial Cell Density and Retinal Nerve Fiber Layer Thickness in Primary Open Angle Glaucoma. J Saidu Med Coll Swat 2021;11(3):137-41. doi.org/10.52206/jsmc.2021.11.3.647

INTRODUCTION

Glaucoma is a disease of optic nerve causing optic nerve degeneration associated with raised IOP, with optic nerve head cupping, and peripheral visual field loss¹. Primary open angle glaucoma is subset of glaucoma with open angle of anterior chamber on gonioscopy and no other underlying cause.

Corneal endothelium is a single hexagonal shaped layer facing toward aqueous humor. These cells have no mitotic activity in vivo. Losses of endothelium cell are compensated by hyperplasia of remaining cells². The corneal endothelium density and morphology are studied with specular microscopy.

Specular Microscopy is a noninvasive technique that is used to study corneal endothelial cells. Normal endothelium count in the sub-continent population is 2408±274 cell/mm, while in the Japanese it is 3749±407 cell/mm at the age of 40 years and above². With Specular microscope the examination of corneal endothelial cell density is possible in detail. At birth the endothelial cell count is between 4000-5000 cells/mm². With age there is

a decline in the cell count; at the age of 40 and above it comes down to 2000-3000 cells/mm².

Endothelial cell count below 500 cells/mm² poses a risk for normal corneal endothelial function³. Other causes of loss of corneal endothelial density include Fuch's corneal endothelial dystrophy, post-operative aphakic or pseudophakic bullous keratopathy, traumatic endothelial decompensation, iridocorneal endothelial syndrome, refractory glaucoma and herpes simplex virus endotheliitis⁴.

In Glaucoma or Ocular Hypertension, the corneal endothelial density (CED) can be affected directly by the high IOP or by congenital anomaly of endothelium or by anti-glaucoma medication toxicity^{5,6}.

Nerve fiber layer of the retina is composed of ganglion cells. Glaucomatous structural changes occurring in RNFL precede the functional changes. The analysis of these structural changes is facilitated by color fundus images and the Optical Coherence Tomography (OCT). These diagnostic tools are used for assessment quantitative and qualitative damage of glaucoma and optic neuropathy⁷.

Optical coherence tomography (OCT) is a non-invasive diagnostic procedure to assess RNFL, macula and optic nerve head. The normal non glaucomatous eye has RNFL thickness of 80 microns or greater, whereas 70-79 microns

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Received: July 20th, 2020 Accepted: May 05th, 2021

thickness of RNLF is suspicious while 60-69 microns thickness of RNLF is glaucomatous in 95% of cases⁸.

ISNT Rule: Inferior thickness > Superior > Nasal > Temporal.

It is an easy ruler to remember. Normally the neuro retinal rim of the optic nerve head is thickest

inferiorly and thinnest temporally. When the optic nerve doesn't follow this rule, it may have glaucomatous damage, but to detect early glaucoma it may not be very effective⁹.

The purpose of the study was to find out the role of open angle glaucoma on corneal endothelium cell density and thickness of retinal nerve fiber layer.

Figure-1 ISNT Rule in normal eye (RNFL in um)

Figure-2. Effect of IOP on corneal endothelium and nerve fiber layer

MATERIALS AND METHODS:

It was a prospective study carried out in the Department of Ophthalmology of Khyber Teaching Hospital, Peshawar from April 2015 to December 2019. Sample size was calculated to be 112 keeping prevalence of open angle glaucoma as 7.1%¹⁰ in Pakistan with a confidence level of 95% and keeping margin of error 5% using WHO sample size calculation. Open angle

glaucoma Patients were included from the outpatient department of ophthalmology of Khyber Teaching Hospital Peshawar through consecutive non-probability sampling method. Written informed consent for the study were taken from all patients. Patients with open angle glaucoma were included with no prior anti-glaucoma treatment taken. For diagnosis of glaucoma all patients, undergone a detail anterior

examination, measurement of intraocular pressure, visual fields (Humphery 30x2) and OCT (Multimodality imaging Heidelberg Spectralis) for glaucoma. Other causes of glaucoma like angle closure, neovascular glaucoma, pseudoexfoliative glaucoma, phacomorphic glaucoma or glaucoma due to any other reason other than Primary Open angle glaucoma were excluded from the study as all these would have acted as confounders to produce bias in the study results. To observe the status of corneal endothelium specular microscopy was performed. To determine the thickness of RNFL, OCT was undertaken. These results were compared to normal age matched database.

Corneal endothelial cells including pachymetry were evaluated through a non-contact specular microscope (specular microscope Topcon SP- 1P and Konan Medical). The number of endothelial cells of cornea (Endothelial corneal Density-ECD), cellular volume was assessed in the central region. Several endothelial cells photographs were taken by the single ophthalmologist and the average value of the two best photographed readings was calculated. The average was

calculated from three measurements for statistical analysis. In all cases intraocular pressure was recorded by using Goldmann applanation tonometer (HAAG STREIT BER H03 Swiss made) at different times a day (9:00 am, 12:00 noon, 2:00 pm 5:00pm). The OCT of RNFL were obtained by using Heidelberg Spectralis OCT machine.

RESULTS

A total of one hundred (112) eyes diagnosed as POAG were enrolled in the study. The mean age of patients were 54.65 ± 16.54 years ranging from 36 years to 67 years. Most of the patients were above 50 years (86.61%) as open angle glaucoma is an age-related disease. Out of 112 patients 57.14% were male and 42.85% were female as shown in the table 1. The mean CED on specular microscopy was 2250 cell/mm² as compared to normal age population matched value of 2725 cell/mm². This showed a loss of 17.12 %. The mean RNFL thickness was 62 microns as compared to normal age population value of 95 micron with a loss of 34.73% as shown in table 2.

Table 1. Demographic distribution of patients (n=112)

Age Range (Years)	Male	%age	Female	%age
31-40 Years	2	1.80%	2	1.80%
41-50 Years	7	6.25%	4	3.57%
51-60 Years	33	29.46%	21	18.75%
61-70 Years	22	19.64%	21	18.75%
Total	64	57.14%	48	42.85%

Table 2. Loss of corneal endothelial cells and NFL layer thickness

State of eyes	Mean Specular Microscopy (Corneal Endothelium cells/mm ²)			Mean NFL Thickness (OCT) (in μ m)		
	Patients	Normal	Loss %	Patients	Normal	Loss %
POAG (n=112)	2250 (n=112)	2715 (n=112)	17.12%	62 (n=112)	95 (n=112)	34.73%

DISCUSSION

Several studies have been conducted employing specular microscopy to examine the CED and loss of nerve fiber layer of the retina in POAG separately. Current study was undertaken to find out the relationship between the loss of corneal endothelial cells and nerve fiber layer thickness in POAG together. Normally there are 87 cell loss/mm² per decade or 0.3% loss per year¹¹.

Corneal endothelium cell loss has been reported in POAG (Gagnon) and normal tension glaucoma (NTG) and ocular hypertension (OHT). The association between raised IOP and endothelial cell loss has been reported by Cho SW et al¹², where the mean CED was 2370.5 ± 392.3 Cells/mm² in POAG and 2723.6 ± 300.6 cells/mm² in the normal age matched population. This showed a lower ECD in eyes with POAG (12.96 %) than normal group. In our study the CED was 2250 cells/mm² in POAG as compared to 2715 cells/mm² in the normal age group with a loss of 17.12%.

Optic neuropathy and endothelial cell loss or damage has been reported by Lee JW et al. In their study the endothelial cell count was lower in POAG (2530 ± 320.4)¹³. Changes and reduction in corneal endothelial cell density in open angle glaucoma have been reported in other studies^{14,15}. Knorr et al in their study showed a 31% reduction of corneal endothelial cell density in open angle glaucoma¹⁶.

In the study of Urban B and Bakunowicz A, the CED was significantly lower in eyes with OAG, being 2639.5 cells/mm² as compared to 2955 cells/mm² in the control group (10.69%)¹⁷. In the study of Prasannakumary C et al¹⁸, the mean endothelial cell density in patients with POAG was found to be lower in right eye than in left eye. There is loss of 8.52% in right eye while 8.03 % in left eye.

All these studies confirmed the loss of CED in open angle glaucoma. The hypothesis for corneal endothelial damage in glaucoma and ocular hypertension was that this damage is due to elevated IOP and medication induced toxicity. As far as loss of thickness of retinal nerve fiber layer (RNFL) is concerned, it has been reported in raised IOP. In normal eyes the RNFL loss is -0.52 um/year¹⁹.

Interestingly thin RNFL has been reported in ocular hypertensive eyes with thinner corneas, whereas ocular hypertensive eyes with thick and normal cornea had normal nerve fiber layer thickness.

In the study by Tarek A et al the mean RNFL thickness was 97.2 ± 9.24 um in healthy subjects, while it was thinner being 60.2 ± 15.9 um in OAG eyes²⁰. The mean loss of RNFL was 38.14 % which is comparable to our study where it was 34.73% in POAG. In the study of Gyatsho et al, OCT detected RNFL thickness differences in POAG, OHT and normal age matched controls. It was observed that the upper, lower and global RNFL measurements were thinner in OHT than normal, and in POAG compared with OHT²¹.

In the study of Christopher B et al reported that the retinal nerve fiber layer was significantly thinner in patients with ocular hypertension in comparison to normal eyes as 72.8 um and 85 um respectively; in the inferior quadrant it was 84.8 um Vs. 107.6 um and in the nasal quadrant 44 um Vs. 61.8 um respectively. In the same study RNFL was found to be thinner in eyes with glaucoma than in OHT and normal eyes in all quadrants²².

In the study of Maria P et al, the RNFL parameters were better in differentiating between normal and ocular hypertensive eyes than optic nerve head (ONH) parameters. The average control group nerve fiber layer thickness was 106 ± 11.5 um, whereas 84 ± 12.8 um in POAG with a loss of 20.75%²³.

Many studies including our study confirmed the loss of retinal nerve fiber layer thickness in patients with open angle glaucoma. Based on the findings of this study our observation is that in POAG, the corneal endothelial cells and nerve fiber layer are affected. The mechanism for this damage might be raised IOP, ischemia, drugs toxicity and toxins in ocular fluids.

CONCLUSION

In this study observation was that loss of both NFL thickness and CED is associated with POAG.

Recommendations

1. Along with OCT and pachymetry, specular microscopy is suggested as a part of glaucoma investigation.
2. All eyes labeled POAG must be evaluated for these parameters including CED loss before anterior segment surgery to avoid corneal endothelium decompensation and to be managed properly.

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DATA SHARING STATEMENT: The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CONFLICT OF INTEREST: Authors declared no conflict of interest.

GRANTED SUPPORT AND FINANCIAL DISCLOSURE: Nil

AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under

Khan BS: Concept and design of study, Collection of data, statistical analysis

Nawaz A: Writing of manuscript, critical review of manuscript

Ahmad I: Analysis and interpretation of data, statistical analysis

Shah Z: Data collection, bibliography

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.