Corneal Endothelial Cell Density Changes In Diabetic And Non-Diabetic Eyes In Grade 2 And Grade 3 Nuclear Sclerosis Undergoing Phacoemulsification

Dr. Krushnadas M. Sarate*, Dr. Darshana B. Rathod, Dr. Harshal D. Sahare*****

*Senior Resident In SRTR Medical College Ambejogai, **Associate Professor In TNMC & BYL Nair Hospital, Mumbai, ***Senior Resident In K.B. Bhabha Hospital, Bandra, Mumbai

Abstract: Background: Corneal endothelial cells are susceptible to mechanical trauma from ultrasound energy during phacoemulsification. Several studies have reported various results of phacoemulsification effect on corneal endothelial cells between diabetic and non-diabetic patients due to stressful events. Present study was aimed to evaluate corneal endothelial density, hexagonality and Central Corneal Thickness (CCT) changes between diabetic and non-diabetic patients at early postoperative period and 1 month after phacoemulsification. Material And Methods: Specular microscopy examinations prior to phacoemulsification and at early postoperative period and 1 months after phacoemulsification were performed on diabetic and non-diabetic groups in grade 2 and grade 3 nuclear sclerosis. Later the changes in endothelial density, the percentage of hexagonality, and Central corneal thickness were evaluated. Result: Mean age of 120 study sample was 58.45 years (standard deviation – 8.498 years), with the highest 74 years and lowest 43 years. There were 53 (44%) females and 67 (56%) males in the study. 42 (35%) samples were from 51-60 years age group followed by 37 (30.83%) subjects in 61-70 years age group. Mean corneal endothelial cell density decreases after cataract surgery in comparison with pre-operative density among study samples. Mean pre-operative corneal endothelial cell density was lower in diabetics in comparison with non-diabetics, and the difference was statistically significant. Cell density count decreases after cataract surgery in both groups with significant difference between two groups. Mean corneal endothelial cell morphology (hexagonal cell percentage) decreases after cataract surgery in comparison with pre-operative density among study samples. Central corneal thickness increases in early postoperative period followed by normalisation at day 30. Conclusion: Diabetic group showed greater hexagonality decrease compared to non-diabetic group at 1 month after phacoemulsification. It is suggested that diabetic corneal endothelium requires additional care and protective measures during cataract surgery to minimize surgical trauma. There were no statistically significant differences in the endothelial loss and Central corneal thickness changes between the diabetic and non-diabetic group at 1 month follow up after phacoemulsification. [Sarate K Natl J Integr Res Med, 2022; 13(1): 16 -22, Published on 26/01/2022]

Key Words: Phacoemulsification, Corneal Endothelial Cell Density, Corneal Endothelial Cell Hexagonality, Central Corneal Thickness, Diabetic And Nondiabetic

Author for correspondence: Sarate Krushnadas Madhavrao, Senior Resident In SRTR Medical College Ambejogai E-Mail: sangovind84@gmail.com, Mobile: 8329116799

Introduction: Phacoemulsification focuses on rapid visual rehabilitation and minimum surgically induced astigmatism. Manual small incision cataract surgery is an alternative technique to phacoemulsification which gives comparable results and is cost-effective[1].

The corneal endothelium that lines the posterior corneal surface is derived from the neural crest during embryologic development. Density of corneal endothelial cells are maximum at birth approx. 6000 cells/mm^2 but the number slowly and steadily keeps on declining after that. A minimal numerical density of >500 cells/mm^2 is required to sustain the pumping activity of the endothelium[2]. The corneal endothelium is essential for maintenance of normal corneal hydration, thickness, and transparency. The dehydrated state of cornea can be monitored by measurement of endothelial cell counts. Loss or damage of endothelial cells leads to an increase in corneal thickness (edema) which may ultimately induce corneal decompensation and loss of vision[3].

Hyperglycemia in diabetic patients causes metabolic stress which can lead to lower endothelial cell density and greater pleomorphism and polymegathism. Specular microscopy is an important noninvasive tool which gives a morphological analysis of the corneal endothelial cell layer[4]. The response and effect of stress and trauma of cataract surgery on endothelial cell could not have been so well documented if it was not for the advent of specular microscopy[5].

Hence, this study was undertaken to assess the stability and vulnerability of the corneal endothelium to avoid postoperative damage to cornea and reduce corneal edema to retain normal corneal function.

Material & Methods: Present study was Prospective cohort study conducted in department of Ophthalmology, at XXX medical college & hospital, XXX, India. Study duration was of 2 years (July 2018 to June 2019).

Study was approved by institutional ethical committee.

Sample Size: 60 in each group by using medcalc statistical software. The sample size was calculated taking the significant change in corneal endothelial cell density (ECD), to detect a difference in mean change of its value, to be 112 cells per square millimeter between the two groups, that is, diabetic group, with standard deviation (SD) 211 and non-diabetic group, with SD: 194 (Hugod M et al)6 and taking power of study to be 80%, then the sample size comes out to be 53 for each group. Taking a follow-up loss of 10%, the Sample size becomes 58.3 (~60) per group, that is, a total of 120 individuals.

Sampling Unit: Sampling unit was "individual"
Sampling Technique: Convenient Sampling technique.

Inclusion Criteria: Age more than 18 years. Pre-operative endothelial cell counts more than 1800 cell/mm2

Exclusion Criteria: Previous history of ocular surgery, ocular trauma, corneal pathology. Contact lens users or intra ocular inflammation. Nuclear sclerosis grade IV or more. Nuclear sclerosis grade 1 or other types of morphological cataract without nuclear sclerosis grade 2 and grade 3. Hba1c more than 7.

Results: Mean age of 120 study sample was 58.45 years (standard deviation – 8.498 years), with the highest 74 years and lowest 43 years. There were 53 (44%) females and 67 (56%) males in the study. 42 (35%) samples were from 51-60 years age group followed by 37 (30.83%) subjects in 61-70 years age group.

Table 1: Corneal Endothelial Cell Density Changes

Descriptive Statistics				
	Group	Mean	Std. Deviation	N
Pre-Operative Endothelial Cell Density (cell/mm^2)	Diabetic	2406.53	187.962	60
	Non-Diabetic	2525.00	119.703	60
	Total	2465.77	167.806	120
Day1 - EndothelialCell Density (cell/mm^2)	Diabetic	2172.95	182.485	60
	Non-Diabetic	2301.60	116.646	60
	Total	2237.27	165.617	120
Day 30 - Endothelial Cell Density (cell/mm^2)	Diabetic	2047.25	171.400	60
	Non-Diabetic	2198.82	110.309	60
	Total	2123.03	162.450	120

Table 2: Tests Of Between-Subjects Effects

Measure: Measure_1 Transformed Variable: Average						
Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	1.864E9	1	1.864E9	2.773E4	.000	.996
GROUP	1589484.003	1	1589484.003	23.647	.000	.167
Error	7931606.106	118	67217.001			

Mean corneal endothelial cell density decreases after cataract surgery in comparison with pre-operative density among study samples. (P=0.000)

Table 3: Levene's Test Of Equality Of Error Variancesa

Duration	F	df1	df2	Sig.
Pre-operative	16.647	1	118	.000
Day 1	15.972	1	118	.000
Day 30	16.332	1	118	.000
Tests the null hypothesis that the error variance of the dependent variable is equal across groups				
a. Design: Intercept + GROUP Within Subjects Design: factor1				

Mean pre-operative corneal endothelial cell density was lower in diabetics in comparison with non-diabetics, and the difference was statistically significant. Cell density count decreases after cataract surgery in both groups with significant difference between two groups. (p=0.000).

Table 4: Hexagonal Cell Morphology

Descriptive Statistics				
	Group	Mean	Std. Deviation	N
Pre-Operative Hexagonal Cells (%)	Diabetic	57.95	2.527	60
	Non-Diabetic	58.05	2.561	60
	Total	58.00	2.534	120
Day 1 - HexagonalCells (%)	Diabetic	54.95	2.303	60
	Non-Diabetic	55.10	2.391	60
	Total	55.03	2.339	120
Day - 30 Hexagonal Cells (%)	Diabetic	52.10	2.161	60
	Non-Diabetic	51.83	2.195	60
	Total	51.97	2.173	120

Table 5: Tests Of Between-Subjects Effects

Measure: Measure_1 Transformed Variable: Average						
Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	1088890.003	1	1088890.003	7.132E4	.000	.998
GROUP	.003	1	.003	.000	.989	.000
Error	1801.661	118	15.268			

Mean corneal endothelial cell morphology (hexagonal cell percentage) decreases after cataract surgery in comparison with pre-operative density among study samples. (P=0.000).

Table 6: Levene's Test Of Equality Of Error Variances[a]

Duration	F	df1	df2	Sig.
Pre-operative	.018	1	118	.892
Day 1	.048	1	118	.826
Day 30	.057	1	118	.811
Tests the null hypothesis that the error variance of the dependent variable is equal across groups.				
a. Design: Intercept + GROUP Within Subjects Design: factor1				

Mean pre-operative hexagonal cell percentage was similar in diabetics and non- diabetics, and the difference was statistically not significant.

Hexagonal cell percentage decreases after cataract surgery in both groups without any significant difference between two groups. (p>0.05)

Mean central corneal thickness (microns) significantly increases after cataract surgery day 1 due to oedema and inflammatory cell response and again decreases till day 30. (P=0.000).

Table 7: Central Corneal Thickness Changes

Descriptive Statistics				
	Group	Mean	Std. Deviation	N
Pre-Operative Corneal Thickness(Microns)	Diabetic	541.35	7.135	60
	Non-Diabetic	541.32	6.988	60
	Total	541.33	7.032	120
Day 1 - CornealThickness (Microns)	Diabetic	562.53	6.479	60
	Non-Diabetic	562.65	6.671	60
	Total	562.59	6.548	120
Day - 30 CornealThickness (Microns)	Diabetic	548.67	7.182	60
	Non-Diabetic	549.57	6.675	60
	Total	549.12	6.919	120

Table 8: Tests Of Between-Subjects Effects

Measure: Measure_1 Transformed Variable: Average						
Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	1.093E8	1	1.093E8	8.847E5	.000	1.000
GROUP	9.669	1	9.669	.078	.780	.001
Error	14579.261	118	123.553			

Table 9: Levene's Test Of Equality Of Error Variancesa

Duration	F	df1	df2	Sig.
Pre-operative	.005	1	118	.941
Day 1	.001	1	118	.974
Day 30	.275	1	118	.601
Tests the null hypothesis that the error variance of the dependent variable is equal across groups.				
a. Design: Intercept + GROUP Within Subjects Design: factor1				

Mean pre-operative central corneal thickness (microns) was similar in diabetics and non-diabetics, and the difference was statistically not significant. Central corneal thickness increases on day 1 and fall till day 30 after cataract surgery in both groups without any significant difference between two groups (p>0.05).

Discussion: Several studies have been conducted to study the effect of cataract surgery on the corneal endothelium by various techniques (conventional extracapsular cataract extraction, small incision cataract surgery, and phacoemulsification). All these studies have shown a decline in the endothelial status after surgery. However, there are only a few studies which have compared these changes with patients with diabetes.

The largest study was conducted by Morikubo et al[7] in 2000–2002, which included 186 eyes (93 in each group). We enrolled 120 eyes in the study sample. The mean age in our study sample was 58.45 years (standard deviation – 8.498 years), with the highest 74 years and lowest 43 years.

There were 53 (44%) females and 67 (56%) males in the study. 42(35%) samples were from 51-60 years age group followed by 37 (30.83%) subjects in 61-70 years age group. In a study by Dandaliya et al.[8] in which 50 patients with type II diabetes (Group I) were enrolled, of which 16 (32%) were male and 34 (68%) females. The mean age of the patients was 57.78 $\pm$ 9.54 (age range 35 to 72).

Whereas control group (non-diabetic) included 21(42%) male and 29 (58%) females. Their mean age was 61.04 $\pm$ 7.45 (age range 41 to 77). The difference in age between both the groups was statistically not significant (P = 0.669). This is similar to our study in which showed mean age of 58.80 years in diabetic patients and 58.10 years in non-diabetic patients and p value showed no statistical significance between the two groups.

There are several studies which reported that diabetic patients have various corneal abnormalities such as increased CCT, reduced ECD, lower corneal sensitivity and increased permeability, low hexagonality and increased percentage of CV[9]. The mean ECD loss was statistically significant between both groups in our study. Previous studies reported endothelial cell loss after cataract surgery[10]. Hugod et al[6] reported a mean loss in ECD was 6.2% in patients with diabetes but only 1.4% in the non-diabetic controls at the end of 3 months after surgery.

Morikubo et al[7] reported 3.2% loss in mean ECD in non-diabetes patients and 7.2% in patients with diabetes at postoperative 1 month follow up visit. Dick etal[11] had shown that endothelial cell loss was maximum at early postoperative period (7.9%)and 6.7% after 6 months.

In our study it was seen that Mean pre-operative corneal endothelial cell density was lower in diabetics in comparison with non-diabetics, and the difference was statistically significant. Cell density count decreases after cataract surgery in both groups with significant dfference between two groups. (p=0.000).

This higher loss in ECD might be explained by fragility of corneal endothelium caused by several metabolic mechanisms in patients with diabetes.

The fragility of diabetic corneal endothelial cells increases due to enhanced polyol pathway and accumulated sugar alcohol in cells. The suppression of Na+-K+ ATPase of the corneal endothelium cells in diabetic patients causes morphological and functional changes of the endothelial cells[12]. Furthermore, accumulation of advanced glycation end products (AGEs) in diabetic cornea causes oxidative DNA damage which suggests apoptotic damage of corneal endothelial cell in diabetic patient[13]. The duration of diabetes mellitus and blood glucose level have proven to be associated with the severity of corneal damage caused by phacoemulsification.

Study reported by Dandaliya et al [8] showed decrease in ECD in both the groups which was higher in group I and there was a steep decline in mean ECD on day 1 post operatively. Wright et al[15]Thakur SKD et al[14] also reported similar finding.

Our study also showed Mean corneal endothelial cell morphology (hexagonal cell percentage) decreases after cataract surgery in comparison with pre-operative density among study samples (P=0.000). Mean pre-operative hexagonal cell percentage was similar in diabetics and non-diabetics, and the difference was statistically not significant. Hexagonal cell percentage decreases after cataract surgery in both groups without any significant difference between two groups (p>0.05).

In study conducted by Budiman[16], there was a statistically significant difference in mean hexagonality percentage at 4 weeks after surgery in the diabetic group. Hugod et al[6] reported a similar result that there was a greater hexagonality decrease in diabetic patients compared to non-diabetic patients. Endothelial density measurement alone was not sufficient to evaluate the function of corneal endothelial cells after intraocular surgery.

Polymegathism represented by the coefficient of variation and polymorphism represented by hexagonality are more sensitive to evaluate whether the corneal endothelial is in a state of stress or not. In their study[16], a greater decrease of hexagonality percentage in diabetic group4-weeks after surgery indicates corneal endothelial healing response, which could be longer than 4 weeks after surgery in diabetic patients. It might be necessary to follow up diabetic patients longer than 4 weeks after phacoemulsification.

When structural changes occur in endothelial cells, the process to regain the cell to its normal and stable hexagonal shape is noteasy.

Hexagonality repair in diabetic patients may take more than 3 months. Uniform hexagonal patterns in corneal endothelial cells create a stable structure. The changes in hexagonality could lead to an unstable layer of corneal endothelial cells[6].

Due to their inability to regenerate, corneal endothelial cells stretch-and cover surrounding areas after surgery. That is the reason why CV percentage usually increases and hexagonality is usually decreased after surgery. However, after the endothelial cells are fully recovered, the CV and hexagonality percentages return to their former values. CV percentage increases in 1 day and reaches a peak at 1 week after surgery and then decreases slowly until 3 months after surgery.In diabetic patients, this process could be longer. Duration of diabetes and glycemic control can affect theresults[17].

In a study conducted by Hossam et al[18] the mean preoperative CV in diabetic patients was 39.84 ±5.30% and that in non-diabetic patients was

41.03 ±5.97 %, whereas the mean preoperative CCT in diabetic patients was 512.56 ± 37.81 µm and that in non- diabetic patients was 507.20 ± 32.18 µm. These results are similar to those of Schultz et al.[19] and Hugod et al.[6], who did not find any difference with regard to preoperative ECD between diabetic patients and controls; however, all these studies had a sample size of around 70 or less. Schultz et al.[19] investigated corneal endothelial changes in type 1 and type 2 diabetes.

They found a significantly higher CV and a significant decrease in the percentage of hexagonal cells in the diabetic group. In both studies, the level of glycemic control was not indicated. Some recent studies have supported these early findings. Su et al.[20] designed a population based cross-sectional study including 3239 eyes and examined the relationship of diabetes with CCT.

They found that diabetes is associated with greater CCT, independent of age, sex, and intra ocular pressure (IOP) levels. The patients with diabetes in this study had poor glycemic control (HbA1c 8.4%), which could explain why they were able to detect a difference in CCT between diabetic and non-diabetic groups. Inoue et al.[21] investigated corneal endothelial structure and corneal thickness in 99 eyes with type 2 diabetes and97 control eyes without diabetes. They found a decrease in cell density and an increase in CV and concluded that the corneal endothelial cell structure was damaged.

Our study showed that Mean pre-operative central corneal thickness (microns) was similar in diabetics and non-diabetics, and the difference was statistically not significant. Central corneal thickness increases on day 1 and fall till day 30 after cataract surgery in both groups without any significant difference between two groups ($p>0.05$).

Conclusion: The surgical trauma is reflected by decrease amount of corneal endothelial cells, which is higher in diabetic patients who have lower capability in the process of repair. The loss of endothelial cells is responded promptly into enlargement of remaining cells and attempts to cover-up the gap, and this shows a short- term increase in cell size and decrease in the percentage of hexagonal cells. Corneal endothelium in patients with diabetes is more prone to surgical trauma than normal corneal endothelium and showed slow recovery fashion postoperatively. This might be due to metabolic stressful events occurring in corneal endothelial stroma.

So it is important to choose proper timing with good glycemic status to perform cataract surgery in diabetic patient. It is suggested that diabetic corneal endothelium requires additional care and protective measures during cataract surgery to minimize surgical trauma.

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Conflict of interest: None
Funding: None
Cite this Article as: Sarate K, Rathod D, Sahare H. Corneal Endothelial Cell Density Changes In Diabetic And Non-Diabetic Eyes In Grade 2 And Grade 3 Nuclear Sclerosis Undergoing Phacoemulsification. Natl J Integr Res Med 2022; Vol.13(1): 16 -22