Corneal Endothelial Cells Changes after Cataract Extraction by Phacoemulsification in Patients with Type 2 Diabetes Mellitus

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Abstract: Background: The functions of the cornea endothelium are to allow nutrients to pass to the outer layers of the cornea, and to prevent the stroma from being overloaded with water by pumping it into the aqueous. **Aim:** The purpose of the current work is to study the corneal endothelium cell changes induced by phacoemulsification in patients with type 2 diabetes mellitus. **Patients and methods:** 40 eyes of 40 patients were chosen from ophthalmology clinic at Tanta University Hospital. The patients were divided into two groups: Group (I): 20 eyes of 20 patients were taken from age groups 50-70 years, diagnosed with type II diabetes, and complicated cataract. Group (II): 20 eyes of 20 patients were taken from age matched groups and have senile cataract. **Results**: There was statistically significant difference between the two groups as regards endothelial cell density, coefficient of variation, central corneal thickness and hexagonality. **Conclusions:** Despite good glycemic control and no corneal abnormalities before surgery, the endothelium in diabetic subjects is more vulnerable to surgical trauma.
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1. Introduction

The corneal endothelium is a single layer of regularly arranged polygonal cells covering the posterior surface of the cornea. A minimum level of 400 to 700 cells/mm² is required for maintenance of normal corneal endothelial function. [1]Corneal edema and decompensation occurs when cell density falls to 500 cells/mm² or below. [2]When endothelial function fails aqueous humor diffuses into the corneal stroma and produces corneal swelling and thickening. Therefore corneal hydration control is the most important index of corneal endothelial cell function. [3]

The corneal endothelium of a patient with diabetes mellitus has been shown to exhibit polymegathism and pleomorphism. [4,5] However, the changes are more difficult to differentiate in patients with Type 2 diabetes mellitus, as these changes naturally occur with increasing age too. [5] The main two functions of the corneal endothelium are to allow nutrients to pass to the outer layers of the cornea, and to prevent the stroma from being overloaded with water by pumping it from the stroma into the aqueous. Corneal endothelial function is decreased in patients with diabetes mellitus, more markedly in eyes presenting with retinopathy and/or with abnormal glucose levels. [6]

Cataract is considered a major cause of visual impairment in diabetic patients as the incidence and progression of cataract is elevated in patients with diabetes mellitus. [7] The association between diabetes and cataract formation has been shown in clinical epidemiological and basic research studies. Even though cataract surgery, the most common surgical ophthalmic procedure worldwide, is an effective cure, the elucidation of pathomechanisms to delay or prevent the development of cataract in diabetic patients remains a challenge. [8]

Phacoemulsification is the gold standard for management of cataract. [9] Corneal endothelial cell loss is an inevitable complication following cataract surgery and occurs after any cataract technique. [9-10]The ideal procedure is one that protects the intraocular tissue from surgical damage particularly the corneal endothelium. The mean endothelial count in the normal adult cornea ranges from 2000 to 2500 cell/mm^{2,} and the count continue to decrease with age. Goal is to perform the surgery in such a way that there is minimal corneal endothelial cell loss or complication, irrespective of the hardness of the cataract, anterior chamber depth and corneal health. [10] Factors such as advanced age, increasing infusion volume and increasing the amount of ultrasound energy and phaco time are the main risk factors for corneal endothelial damage. Endothelial changes and alternations of central corneal thickness are considered important parameters of surgical trauma and are indispensable in evaluating the safety of new surgical methods. [10]

Aim and objectives

Thepurpose of the study is to study the corneal endothelium cell changes induced by

phacoemulsification in patients with type 2 diabetes mellitus by non contact specular microscopy.

2. Patients and Methods

This study was conducted as a prospective study. 40 eyes of 40 patients were. chosen from ophthalmology clinic at Tanta University Hospital and scheduled for phacosurgery. The patients were divided into two groups: Group (I): 20 eyes of 20 patients were taken from age groups 50-70 years, diagnosed with type II diabetes, and associated with complicated cataract. Group (II): 20 eyes of 20 patients were taken from age matched groups and have senile cataract. A blood glucose test was done to discover diabetic patients. Informed consent was obtained from all study participants.

Inclusion criteria:

1- Patients from 50 to 70 years old.

2- Patients have type II diabetes mellitus and complicated cataract with no clinically significant macular edema.

3- Endothelial cell count > 2000 cells/mm2.

Exclusion criteria:

1-Endothelial cell count < 2000 cells/mm2.

2- Corneal pathology.

3- Intraocular inflammation.

4- Previous ocular trauma.

5- Previous intraocular surgery.

6- Age younger than 50 years and older than 70 years.

7- Ocular diseases that may affect endothelial cell function as glaucoma, uveitis and pseudoexfoliation syndrome.

8-Intraoperative complication as posterior capsular or zonular rupture, vitreous loss, iris or ciliary body injury, loss of nuclear material into vitreous, suprachoroidalhemorrhage, and Retrobulbar hemorrhage.

All patients included in the study were subjected to the following:

A-Full history taking

1- Personal history including: Name, age, sex, occupation, address, and marital status.

2- History of diabetes mellitus: Age of onset, duration and medication.

3- History of any other systemic disease.

4- History of any previous ocular diseases or surgeries.

5- History of argon laser photocoagulation and triamcinolone or anti- vascular endothelial growth factor injections.

B-Examination:

1-Visual acuity assessment, including uncorrected visual acuity and best corrected visual acuity.

2- Slit lamp biomicroscopy.

3- IOP measurement by Goldmannapplanation tonometer.

4-Fundus examination by indirect ophthalmoscopy.

C- Investigations:

1- Ultrasonography including A-scan and B-scan.

2- Preoperative specular microscopy: Central corneal endothelial photographs 0.25x0.55 mm. were measured preoperatively using a noncontact specular microscope Topcon SP-1P (Topcon Corporation, Japan). Evaluation of the central endothelial cell density (CD), coefficient of variation (CV), central corneal thickness (CCT) and percentage of cell hexagonality (HEX).

Follow up:

The follow up regiment was for three months. The patients were examined one day postoperative, and after one week, two weeks, three weeks, one month, two months, and three months.

In Each visit the following was recorded:

- Best corrected visual acuity (BCVA) visual acuity was recorded.
- Slit lamp valuation performed and the following parameters were recorded:
  - Wound status.
  - Cornea for edema and has been graded clinically by OCTET grading system [29]:

1- Transient corneal edema

2- Transient corneal edema with descement membrane folds < 10 folds

3- Transient corneal edema with descement membrane folds >10 folds [29].

- Anterior chamber depth and content.
- Regularity of the pupil.
- Stability of the IOL.
- Intra ocular pressure was measured using Goldmannapplanation tonometer.
- Specular microscopy:

After three months the central endothelial cell density (CD), coefficient of variation (CV), central corneal thickness (CCT) and percentage of cell hexagonality (HEX) were analyzed and comparison of the results of the two groups was done.

Preoperative preparation:

1- Preoperative laboratory investigation including:

Fasting and 2 hours post prandial blood glucose level, serum glycated hemoglobin (HBA1c), Prothrombine time and partial thromboplastine time.

2-Preoperative medications:

- Antibiotics: Cefotax 1 gm vial (Cefotaxime 1 gm vial, Egyptian international pharmaceutical industries corporation, Egypt) intravenous injection before surgery.

- Pupillary dilatation was done by topical application of mydriacyl 1% sterile ophthalmic solution (tropicamide 1% ophthalmic solution, Alcon Laboratories, United Kingdom, Ltd.) eye drops one hour preoperative.
- Local anesthesia:

Phacoemulsification surgery was done under local anesthesia Benox 0.4% sterile ophthalmic solution (Benoxinate hydrochloride 0.4% ophthalmic solution, Egyptian international pharmaceutical industries corporation, Egypt.) was applied three times just before operation with 1-2 minutes interval then peribulbar anesthesia was done with 5 ml. of 2% Mepivacaine hydrochloride 20 mg and Levonordefrin hydrochloride 0.06 mg. (Alexandria Corporation for Pharmaceuticals, Egypt) using a 24G needle towards floor of orbit. The eyelids then were closed and pressure was applied for 5 minute.

Surgical technique:

Disinfection of eyelids with povidone-iodine 10% (Betadine) and draping the eye with a sterile plastic adhesive drape then applying wire speculum and disinfection of the conjunctival sac with providone-iodine 5%. Side port was done by a 20 gauge disposable ophthalmic microviteroretinal blade (MVR) at 2 o'clock position. Injection of viscoelastic VISICROM 2% (20 mg Hydroxypropylmethylcellulosesolution/ml, Croma, pharma Gmbh, Austria) through the side port to form the AC and protect the endothelium. Main corneal incision: disposable ophthalmic keratome was used to create a corneal tunnel in the upper temporal quadrant of about 2 mm length and 3 mm width.

Viscoelastic Optiflex (sodium hyaluronate1.4% ophthalmic solution, Moss vision Inc. Ltd., London) was injected to form the AC and to flatten the anterior lens capsule preparing for the capsulorhexis. Capsulorhexis forceps was used to do continuous curvilinear capsulorhexis size about 5.5 - 6 mm.

Hydrodissection was done after washing out the viscoelastic from the AC before starting by a 27 gauge bent tip cannula attached to syringe filled with BSS, the tip of the cannula was advanced under the anterior capsule, slowly and steady stream of fluid is injected to disrupt the adhesions between cortex and capsule. Rotation of the nucleus was done to insure that it was freely mobile and no adhesions still present. Nuclear disassembly: using whitestar signature phacoemulsification system (Abbott Laboratories Inc. Abbott Park, Illinois, USA), standard tip with 15^0 bevel fitted on phaco hand piece were used in all cases. Vertical chopping was done using the following parameters; power 60% burst mode, vacuum: 350 mmHg, aspiration flow rate 35 mm/min to hold the nucleus firmly, the vertical chopper introduced from the side port and penetrate the nucleus vertically producing a vertical separation then we rotates the nucleus and repeat the maneuver then emulsification of the chopped fragments was done with the same parameters. Irrigation and aspiration (I/A) the cortical matter was done by coaxial I/A. Injection of viscoelastic Optiflex (sodium hyaluronate1.4% ophthalmic solution, Moss vision Inc. Ltd., London) was used to reform and stabilize the surgical planes and fill the capsular bag. IOL implantation: posterior chamber 6 mm foldable hydrophobic intraocular lens (Sensar three piece IOL, Abbott optics) was inserted with the injector system through the 3 mm incision into the bag then washing out of viscoelastic. Stromal hydration of the side port and the main wound it helps to reform the globe. Topical antibiotic Zymar sterile ophthalmic solution (Gatifloxacine 0.3% sterile ophthalmic solution, Allergan plc. USA) was instilled into the eye then covering the eye with eye pad. All cases underwent surgery by the same experienced surgeon and the amount of fluid used ranged from 80 – 150 ml Ringer's solution, with no drugs used in the fluid and no drugs used intracameral.

3. Results

In group I mean age is 65.05 ± 4.74 years, while in group II mean age is 62.10 ± 7.12 years. There is no statistically significant difference between the two groups as regards age. [Table 1]

Table (1): Comparison between the two studied groups according to age:

Age	Non diabetic	Diabetic
Range	50 – 70	55 – 70
Mean ± SD	62.10 ± 7.12	65.05 ± 4.74
T. test	2.378	
P. value	0.131	

Endothelial cell density (CD):

In group I the mean change in cell density at three months after surgery is 356.3 ± 324.5 cell/mm2, while in group II is 46.9 ± 35.21 cell/mm2, There is statistically significant difference between the two groups as regards endothelial cell density change. [Table 2]

Table (2): Comparison between the two studied groups according to endothelial cell density change (CD):

Cell density	Non diabetic	Diabetic
Range	4 – 145	39 – 962
Mean ± SD	46.9 ± 35.21	356.3 ± 324.5
T. test	17.967	
P. value	0.001*	

Coefficient of variation (CV):

In group I the mean change in coefficient of variation at three months after surgery is 4.8 ± 3.89%, while in group II is 1.0 ± 1.12%. There is statistically significant difference between the two groups as regards postoperative coefficient of variation change. [Table 3]

Table (3): Comparison between the two studied groups according to change in coefficient of variation (CV):

Coefficient of variation %	Non diabetic	Diabetic
Range	0.0-4.0	0.0-15.0
Mean ± SD	1.0 ± 1.12	4.8 ± 3.89
T. test	17.632	
P. value	0.001*	

Central corneal thickness (CCT):

In group I the mean change in central corneal thickness at three months after surgery is 13.50 ± 4.08 µm, while in group II is 9.75 ± 6.86 µm. There is statistically significant difference between the two groups as regards postoperative central corneal thickness change. [Table 4]

Table (4): Comparison between the two studied groups according to change in central corneal thickness (CCT):

Central corneal thickness	Non diabetic	Diabetic
Range	-6.0 – 19.0	9.0 – 26.0
Mean ± SD	9.75 ± 6.86	13.50 ± 4.08
T. test	4.414	
P. value	0.042*	

Hexagonality:

In group I the mean change in hexagonality at three months after surgery is -10.45 ± 5.23 %, while in group II is -6.55 ± 4.52%. There is statistically significant difference between the two groups as regards postoperative change in hexagonality. [Table 5]

Table (5): Comparison between the two studied groups according to change in hexagonality:

Hexagonality %	Non diabetic	Diabetic
Range	-19.0 – -1.0	-26.0 – -1.0
Mean ± SD	-6.55 ± 4.52	-10.45 ± 5.23
T. test	6.366	
P. value	0.016*	

Duration of diabetes:

In group I There is statistically significant correlation between the duration of diabetes mellitus and the change in corneal endothelial cells as regards postoperative endothelial cell density change, coefficient of variation change, central corneal thickness change, and hexagonality change. [Table 7] [Figures 11,12,13,14]

Table (7): correlation between the duration of diabetes and the change of endothelial cells:

	Duration of Diabetes	
	T.test	**P.value**
Cell density	0.737	0.001*
Coefficient of variation %	0.455	0.044*
Central corneal thickness	0.601	0.005*
Hexagonality %	0.598	0.006*

4. Discussion

Although endothelial cell density is a widely used parameter for the status of the cornea after cataract surgery, it does not reflect the dynamics of the endothelial healing process that occurs in response to surgical trauma. The decrease in cell density reflects the surgical trauma itself, whereas the change in morphology is more closely associated with the process of repair.

In an immediate response to a loss of endothelial cells, the remaining cells enlarge and slide in an attempt to cover the posterior corneal surface fully, and this is reflected in a short term increase in the cell size and a decrease in the percentage of hexagonal cells. When the endothelium is stabilized after a period of rearrangement, the CV and the hexagonality shift toward the preoperative status. [11-12]

This process of repair might be delayed or diminished in diabetes. Postoperatively the coefficient of variation is significantly increased in the diabetic group compared to the non-diabetic group, which reveals that the endothelial cells have not yet returned to the preoperative status of steady state.

In this study a significantly greater corneal endothelial cell loss was observed in diabetic subjects compared with non-diabetic subjects after phacoemulsification with intraocular lens implantation. The data reflect an increased vulnerability of the corneal endothelium in patients with diabetes with greater loss of cells.

Several other studies have indicated that the endothelium of diabetic subjects might be more vulnerable to surgical traumas than that of non-diabetic subjects. **Morikubo et al** [13] compared corneal thickness and morphology in 93 eyes in patients with type 2 diabetes with 93 eyes in patients without diabetes before and 1 day, 1 week, and 1 month after phacoemulsification. Compared with non-diabetic group, the study found that the central corneal thickness increase observed 1 month after operation was 0.04% in the non-diabetic group 1.6% in the

diabetic group. The increase after 1 month was significantly higher in the diabetic group than in the non-diabetic group (P=.03). The endothelial cell losses occurring 1 month after operation was 3.2%, in the non-diabetic group 7.2% in the diabetic group. The coefficient of variation 1 month after operation was 0.308, and in the non-diabetic group and 0.312 in the diabetic group, without significant differences between the 2 groups, this study uses BSS PLUS (Alcon Laboratories, Inc.) as a perfusion fluid. In our study there is significantly increase in the CV postoperatively in the diabetic group than in the non-diabetic group, and there is significant loss of the endothelial cells by 11.87 % in the diabetic group and 1.57% in the non-diabetic group postoperatively, and our study uses ringer's solution as a perfusion fluid.

A study done by **Schultz et al** [11] to assess the response of endothelium to cataract surgery showed a decrease in the endothelial density over 3 months postoperatively, with an increase in the coefficient of variation, Another study done by **Ventura et al** [14] showed a significant endothelial loss with an increase in the CCT after cataract surgery, the latter returning to normal values within 3 months. Previous studies [15, 16, 17] shown that endothelial cell density decreases 6% to 10% after phacoemulsification for cataract.

In our study there is insignificant increase in the central corneal thickness postoperatively in diabetic patients than in non-diabetics with increase in change of the central corneal thickness 3 months after operation is 9.75 ± 6.86 µm in the non-diabetic group and 13.50 ± 4.08 µm in the diabetic group, this result is supported by other studies as **Mikkel Hugod et al** [18] who made a clinical prospective study including 30 patients with type 2 diabetes and 30 control patients without diabetes scheduled to undergo cataract surgery, There was no statistically significant change in CV or CCT. Visual acuity increased significantly and equally in the 2 groups. The mean decrease in endothelial cell density at 3 months in the diabetic group was 154 cells per square millimeter (6.2%) and 42 cells per square millimeter (1.4%) in the control group. The difference in cell loss between the 2 groups was significant (P = 0.04).

Goebbels and Spitznas [19] performed fluorophotometry of the corneal endothelium before and 4 days, 3 weeks, and 6 weeks after phacoemulsification and intraocular lens implantation, and endothelial permeability was evaluated in the presence or absence of diabetes mellitus. Endothelial permeability did not differ between the diabetic and non-diabetic groups before operation. Markedly increased in both groups 4 days after operation, and recovered 3 weeks after operation in the non-diabetic group but 6 weeks after operation in the diabetic group. This result was consistent with slightly increased corneal thickness of diabetic patients postoperatively 3 months after surgery observed in our study.

On the other hand, **Furuse et al** [20] compared the endothelial cell density, coefficient of variation, and endothelial cell loss 3, 6, and 12 months after extracapsular cataract extraction and intraocular lens implantation between patients with and without diabetic mellitus and observed endothelial cell density decreases of 10% to 20% in both groups, without noticeable differences. This variation in findings between their study and ours may be because extracapsular cataract extraction is more invasive to the cornea than phacoemulsification and masks diabetes mellitus associated differences.

In our study the decrease in corneal endothelial density and increase in coefficient of variation for the diabetic patients were significantly greater than those in the control group. This indicates that diabetic patients are more susceptible to corneal endothelial damage during the phacoemulsification, which might be explained by the fact that the activity in polyol pathway is increased in the diabetic patients, so that additional glucose is transformed into sugar alcohols, and then accumulates in cells. Aldose reductase in the polyol pathway is distributed over the corneal epithelial and endothelial cells, while accumulation of sugar alcohols leads to increased osmotic pressure, rendering corneal endothelial cells more vulnerable. [21, 22]

Morphological abnormalities in the corneal endothelium have been reported to improve after administration of an inhibitor of this enzyme [23, 24] which supports the involvement of this enzyme in the development of corneal endothelial abnormalities in eyes of patients with diabetes mellitus. [23, 24]

It has been suggested that high levels of glucose reduces the corneal ability to control hydration/dehydration, and impairs the activity of the NA^+/K^+ ATPase enzyme in corneal endothelial cells and interferes with the functions of this fluid pump [25]. Such metabolic stress evidently impairs the ability of corneal endothelial cells to resist mechanical stress such as phacoemulsification. Moreover, since glucose concentration in the aqueous humor is frequently increased in diabetic patients on a long term basis, normal glucose metabolism in the cornea is affected resulting in metabolic acidosis in the corneal matrix and subsequent changes in corneal endothelial morphology and function. Among patients undergoing phacoemulsification, loss of corneal endothelial cells is unavoidable due to the mechanical injury caused by repeated insertion and withdrawal of surgical instruments and the heat injury induced by ultrasonic energy. [26]

Hence, proper preoperative treatment regimens should be established for diabetic patients. This combined with careful preoperative assessment of the condition and compensating capacity of the corneal endothelium, proper selection of surgical approach, and minimal duration of phacoemulsification during the procedure, may help to reduce the risk of corneal decompenastion.

In addition to limiting ultrasonic energy to the extent possible, phacoemulsification should be performed within the, capsular bag, and a stable anterior chamber should be maintained. Mechanical injury caused by repeated insertion and withdrawal of surgical instruments should be limited, and high quality irrigation fluid and viscoelastic agents [27,28]. These measures are critically important to reduce the loss of corneal endothelial cells and maximize recovery of visual acuity after the procedure in patients with cataract and concurrent diabetes.

The higher cell loss observed among patients with diabetes might be because of more complicated surgery. In the present study, because of study design, we did not record parameters such as pupil size, or total phaco energy. It is a deficiency of our study. **Zaczek and Zetterstrom** [29] found that surgically induced miosis at the end of the phacoemulsification operation was more pronounced in diabetic subjects and that the entire surgical procedure lasted significantly longer when performed in diabetic eyes. These findings were later supported by **Mirza et al** [30]. Thus; it is likely that these factors have an effect on the corneal endothelium and its recovery after surgery. In summary, maintaining adequate corneal endothelial health poses a particular challenge after phacoemulsification and intraocular lens implantation in diabetic patients.

In our study the change of corneal endothelial cells after phacoemulsification is significantly increases with longer duration of diabetes mellitus in spite of good glycemic control. This results supported by **Lee et al.** [31] investigated corneal endothelial morphology and corneal thickness in 200 insulin-dependent diabetic patients and 100 age-matched healthy controls. They concluded that patients with diabetes had increased CCT and CV and decreased CD and percentage of hexagonal cells, as compared with healthy controls. Those patients with diabetic duration of over 10 years have more corneal morphological abnormalities, especially the coefficient of variation in cell size, compared with the normal subjects. The central corneal thickness was significantly correlated with diabetic duration after controlling for age. Patients with a more than 10-year history of diabetes also had thicker central corneas compared with patients with a diabetic history of less than 10 years. The glycemic condition of the patients with diabetes was not evaluated, but these results might suggest that long duration of diabetes leads to poor corneal status.

Conclusions:

Despite good glycemic control and no corneal abnormalities before surgery, the endothelium in diabetic subjects is more vulnerable to surgical trauma and has a lower capability in the process of repair. Maintaining adequate corneal endothelium health poses a particular challenge after phacoemulsification and intraocular lens implantation in diabetic patients.

These findings should be considered when planning for cataract surgery in patients with diabetes. However, despite significant higher loss of endothelial cells and a significant slower process of cell repair in diabetic subjects, functional ocular status seemed unchanged as judged by CCT. Thus, a sufficient reserve capacity to maintain normal corneal functional status in well controlled patients with diabetes exists during the period of follow up.

Diabetic patients with visually significant cataracts pose unique challenges during surgery, and they may be prone to a more difficult postoperative recovery. However, with careful surgical techniques and appropriate medications after surgery, these patients can do very well and recover excellent vision just like other cataract patients.

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Conflicts of interest:

No conflicts of interest declared.

Authors' Contributions:

All authors had equal role in design, work, statistical analysis and manuscript writing.

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