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Risk factors for corneal endothelial cell loss after phacoemulsification

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Abstract:

PURPOSE: The purpose of this study was to evaluate the changes in corneal endothelial cell density (CECD) occurring after cataract phacoemulsification surgery and identify factors associated with cell loss.

MATERIALS AND METHODS: This was a retrospective study involving patients who underwent cataract phacoemulsification surgery between January 1, 2018, and December 31, 2018, at two private hospitals. Demographic data and biometric parameters were obtained preoperatively. Ultrasound metrics were recorded for each operation, including total on time (TOT), total equivalent power in position 3, and cumulative dissipated energy (CDE). Using corneal specular microscopy, CECD was measured preoperatively and postoperatively at 12, 24, and 36 months. Factors associated with decreased CECD were identified.

RESULTS: This study included 223 eyes of 133 patients. The mean CECD was 2530.03 ± 285.42 cells/mm^2 preoperatively and significantly decreased to 2364.22 ± 386.98 cells/mm^2 at 12 months ($P < 0.001$), 2292.32 ± 319.72 cells/mm^2 at 24 months ($P < 0.001$), and 2242.85 ± 363.65 cells/mm^2 at 36 months ($P < 0.001$). The amount of cell loss was associated with age, gender, preoperative CECD, preoperative anterior chamber depth, lens thickness, TOT, and CDE. Using multivariate analysis, age, preoperative CECD, and TOT were identified as independent predictors for CECD loss 12 months after surgery.

CONCLUSION: The greatest decrease in CECD occurred during the first year after cataract surgery, and the amount of cell loss was influenced by both baseline patient characteristics and ultrasound metrics. Longer-term prospective studies in a larger cohort may yield more information.

Keywords:

Cataract surgery, corneal endothelium, phacoemulsification

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Introduction

Cataract surgery, the most common elective procedure performed worldwide, has the potential to greatly improve visual function and treat blindness. However, as with any surgical procedure, and despite modern phacoemulsification techniques, postoperative complications may occur.[1] The corneal endothelium is particularly vulnerable to injury during cataract surgery and does not have any regenerative ability. As part of this process, the normal hexagonal cell arrangement is disrupted, the remaining cells enlarge to compensate for missing cells, and there is an overall decrease in corneal endothelial cell density (CECD).[2]

Normal CECD is approximately 2500 cells/mm^2, with cell density naturally declining as part of the aging process.[2] However, cataract surgery has been reported to accelerate this process, with some studies recording rates of cell loss >20% within the first 12 months postoperatively.[1,3] Damage to corneal tissue may occur due to a combination of factors, including direct instrumental trauma, exposure to ultrasound energy, free radical formation, and contact with the intraocular lens or nuclear fragments.[4,5] When cell density

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falls below 500 cells/mm^2, there is a high risk of corneal edema and decompensation.[2,6]

At present, there is much variation in factors that have been shown to influence CECD loss after cataract surgery. Patient-related factors, including age,[1,2,7] preoperative anterior chamber depth (ACD),[8] preoperative CECD,[1] axial length,[9] and cataract grade,[2,7] and surgery-related factors, including phacoemulsification energy[1,10] and phacoemulsification time,[11,12] have been implicated in the current literature. However, findings have been limited by relatively short follow-up, with studies generally reporting CECD outcomes at 12 months or less.[2,4,9,10] Furthermore, with the development of modern surgical techniques and technologies, some earlier studies no longer reflect the current practice.[7,10]

The aims of this study were to evaluate the 3-year changes in CECD after cataract phacoemulsification surgery in a contemporary cohort and identify factors affecting cell loss. Understanding these factors may better inform approaches to minimizing corneal endothelial injury intraoperatively and assist in the identification of patients at greater risk of future complications.

Materials and Methods

Study population

This retrospective observational study included patients who underwent cataract phacoemulsification surgery, by a single ophthalmic surgeon, between January 1, 2018, and December 31, 2018. Cataract phacoemulsification was performed using the Alcon Constellation OZil IP system with a 0.9 mm mini-flared 45° Kelman® phaco tip through a 2.75 mm temporal corneal incision. All patients received Alcon SN60WF IOL. All patients attended follow-up during the 3-year postoperative period. Exclusion criteria were patients who had cataract surgery combined with another procedure or those where a superior corneal incision was used. Patients who received toric lenses or other lenses were also excluded.

Data collection

Demographic data were collected on patient gender and age. All patients underwent comprehensive ophthalmic examination 1 week before surgery, where the ocular parameters ACD, axial length (AL), and central corneal thickness (CCT) were measured using IOLMaster 700 (Carl Zeiss, Germany). Ultrasound metrics were obtained from the operative record and included total on time (TOT), total equivalent power in position 3 (TEPP3), and cumulative dissipated energy (CDE).

Corneal specular microscopy was performed on the central cornea preoperatively and postoperatively at 12, 24 and 36 months. CECD was analyzed using an automated noncontact specular microscope (Tomey EM-3000, Nagoya, Japan) and recorded as the number of cells/mm^2. Of the 15 photographs taken by the specular microscope, only the cell density from the clearest image was used. All measurements and assessments were conducted by the same ophthalmic surgeon.

Statistical analysis

Demographic data were analyzed using descriptive statistics. The paired *t*-test was used to assess differences in CECD preoperatively and at 12, 24, and 36 months after surgery.

Differences in corneal endothelial cell loss between groups were evaluated using the independent *t*-test. Pearson's correlation coefficient was used to identify significant associations between the amount of CECD loss at 12, 24, and 36 months, and baseline ocular parameters and ultrasound metrics. Variables with $P < 0.20$ on univariate analysis at 12 months were entered into multiple regression analysis. Backward variable selection was performed to determine the variables independently associated with CECD loss. The sample size was not formally calculated as this was a retrospective cohort study that utilized all available data.[13]

$P < 0.05$ was used to indicate statistical significance. All data were analyzed using IBM SPSS Statistics, version 26.0 (IBM Corp, Armonk, NY, USA).

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Northern Sydney Local Health District Human Research Ethics Committee (2021/PID01969). Informed consent was obtained from all participants.

Results

A total of 223 eyes of 133 patients were included in this study. Baseline characteristics of the study population are shown in Table 1. During the 3-year postoperative period, the number of eyes analyzed was 186 eyes at 12 months, 139 eyes at 24 months, and 107 eyes at 36 months.

The mean CECD was 2530.03 ± 285.42 cells/mm^2 preoperatively. Significant cell loss occurred over each 12-month period, with mean CECD decreasing to 2364.22 ± 386.98 cells/mm^2 at 12 months ($P < 0.001$, paired *t*-test), 2292.32 ± 319.72 cells/mm^2 at 24 months ($P < 0.001$, paired *t*-test), and 2242.85 ± 363.65 cells/mm^2 at 36 months ($P < 0.001$, paired *t*-test). This represented the rates of cell loss of 9.46%, 1.82%, and 2.93% during each subsequent 12-month period after surgery. The

changes in CECD during the 3 years after surgery are shown in Figure 1.

By univariate analysis, factors demonstrating significant correlations with decreased CECD at 12 months were patient age, gender, preoperative CECD, ACD and lens thickness (LT), TOT, and CDE. Factors that were not found to be significant on univariate analysis were TEPP3, preoperative CCT, and preoperative AL. Using multiple regression analysis, the variables independently associated with CECD loss were age ($P < 0.001$), preoperative CECD ($P < 0.001$), and TOT ($P = 0.018$). These results are summarized in Table 2. The final model ($P < 0.001$) explained 21% of the variance in CECD loss at 12 months ($r^2 = 0.21$).

Correlations between mean CECD loss and age, preoperative CECD, and TOT are shown in Figure 2. Preoperative CECD was significantly correlated with the mean CECD at 12 months after surgery ($P < 0.001$).

Table 1: Study population characteristics

Characteristic	N=223
Number of eyes/patients	223/133
Age (years), mean±SD (range)	67.96±7.17 (37–90)
Gender, *n* (%)	
Male	97 (43.5)
Female	126 (56.5)
Eye laterality, *n* (%)	
Right	108 (48.4)
Left	115 (51.6)
CECD (cells/mm^2), mean±SD	2530.03±285.42
ACD (mm), mean±SD	3.11±0.40
LT (mm), mean±SD	4.60±0.39
CCT (μm), mean±SD	544.27±35.36
AL (mm), mean±SD	24.41±1.47
TOT (s), mean±SD (range)	77.44±39.71 (2–331)
TEPP3 (%), mean±SD (range)	16.40±3.36 (10.5–37.7)
CDE, mean±SD (range)	12.92±8.39 (0.93–63.84)

SD=Standard deviation, CECD=Corneal endothelial cell density, ACD=Anterior chamber depth, LT=Lens thickness, CCT=Central corneal thickness, AL=Axial length, TOT=Total on time, TEPP3=Total equivalent power in position 3, CDE=Cumulative dissipated energy

Table 2: Multiple regression analysis of factors affecting corneal endothelial cell density loss

Variable	*B* coefficient (95% CI)	SE	*P*
Age	9.87 (5.70–14.06)	2.11	<0.001
Gender			
Female	Reference		-
Male	36.83 (−21.38–95.05)	29.50	0.213
Preoperative CECD	0.18 (0.08–0.27)	0.05	<0.001
Preoperative ACD	−51.35 (−118.42–15.714)	33.99	0.133
Preoperative LT	11.05 (−62.25–84.36)	37.15	0.766
TOT	0.91 (0.16–1.67)	0.38	0.018
CDE	−1.36 (−9.47–6.75)	4.11	0.741

CI=Confidence interval, SE=Standard error, CECD=Corneal endothelial cell density, ACD=Anterior chamber depth, LT=Lens thickness, TOT=Total on time, CDE=Cumulative dissipated energy

Using univariate analysis, factors significantly associated with CECD loss were identified at 24 months and 36 months postoperatively. The factors influencing cell loss at 24 months were patient age ($P < 0.001$), gender ($P < 0.001$), preoperative ACD ($P = 0.007$), TOT ($P = 0.002$), and CDE ($P = 0.008$). At 36 months, only patient gender was found to be significantly associated with CECD loss ($P = 0.041$).

Discussion

Corneal endothelial cell loss occurring after cataract surgery is well documented.[2,7] However, to the authors' knowledge, the rates of CECD decline over a 3-year timeline have not yet been evaluated, and the current understanding of the patient and surgery-related factors influencing cell loss remains limited.

The amount of reported cell loss occurring after cataract phacoemulsification surgery is highly varied, ranging from 11.6% at 1 month,[12] 7.3% at 12 months,[10] 15.0% at 6 years,[14] and 20.6% after 10 years.[15] The results of our study are comparable to other records of decreased CECD at 12 months postoperatively.[2,9] However, while the amount of cell loss was the greatest within the first year, cell density continued to significantly decline, at 1.82% during the second and 2.93% during the third year after surgery. As the rate of normal CECD decline has been approximated at 0.5%–1% per year,[8] our findings suggest that accelerated corneal endothelial loss after cataract surgery may persist in the long term. This is similar to the adjusted yearly cell loss rates of 2.06%[15] and 2.5%[16] published in two 10-year studies. While the precise mechanisms behind a continued and accelerated CECD decline remain unclear, it has been hypothesized that chronic cell loss may be perpetuated by subclinical inflammation,[15] exposure to vitreous, and alterations in aqueous humor that compromise endothelial cell nutrition.[16]

Of the 10 variables included in the initial univariate analysis, seven were found to demonstrate significant

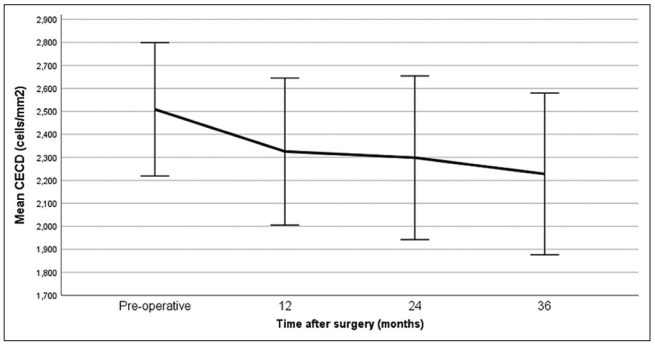

Figure 1: Mean corneal endothelial cell density preoperatively and after surgery. Error bars represent standard errors. CECD = Corneal endothelial cell density

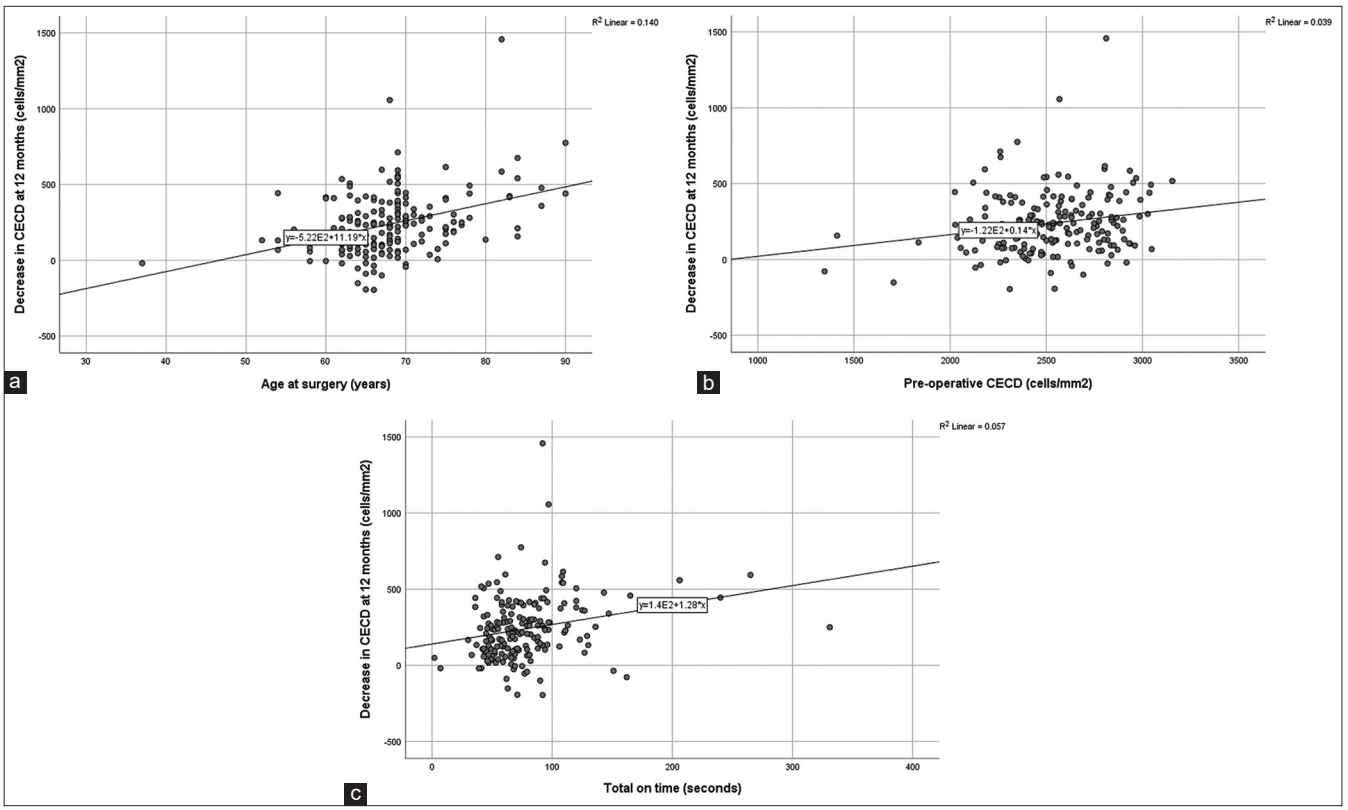

Figure 2: Scatterplots showing mean decreases in CECD against age (a), preoperative CECD (b), and total on time (c). CECD = Corneal endothelial cell density

associations with cell loss at 12 months. Preoperative ACD was first described by Hwang *et al*.[8] to influence CECD, where similarly to the present study, eyes with shallower anterior chambers exhibited higher amounts of cell loss. This is thought to be due to phacoemulsification being conducted in closer proximity to the corneal endothelium, increasing the risk of injury from ultrasound and heat energy, instrumental trauma, and lens fragments.[8] However, the overall evidence on the impact of ACD is unclear, as ACD was not an independent predictor on multivariate analysis, and other studies have not shown any significant association between ACD and cell loss.[9,17]

Similarly, CDE, patient gender, and LT were correlated with corneal endothelial loss at 12 months on univariate analysis but were not retained in the final model. Higher CDE has been correlated with greater corneal endothelial loss in one study,[3] as has higher ultrasound power.[10,12] This may be due to increased heat generation and turbulence within the anterior chamber during phacoemulsification.[3] Our results also identified a positive correlation between LT and cell loss, which has not previously been described, although increasing LT and lens nucleus density have been associated with advancing age and shallow anterior chambers.[9] In this study, while mean cell loss was observed to be higher in males than females, patient gender has consistently been shown not to independently affect CECD in the existing literature.[7,15,16,18]

The final multivariate model contained patient age, preoperative CECD, and TOT as significant factors affecting cell loss. Age has previously been shown to influence postoperative CECD[1,2,19] and has been correlated with higher phacoemulsification energy and cataract grade.[1] This is an important consideration when planning the timing of surgery, as there may be an increased risk of corneal complications in patients of advanced age.[19]

Ultrasound time has also been associated with cell loss in some studies[3,9,10,12] and may indirectly reflect mechanical injury to corneal endothelium. A higher TOT may be associated with factors such as increasing age, LT, and cataract grade.[9] Studies have also demonstrated increased TOT when phacoemulsification is performed by junior surgeons[12] or in the eyes with small pupils. However, in this study, all procedures were performed by the same experienced surgeon, and pupils were adequately dilated.

Preoperative CECD was recently identified as a novel predictive factor for cell loss,[1] despite earlier studies demonstrating no significant association.[2,12,15,16] In the study by Chen *et al*.,[1] the eyes with a preoperative CECD between 1000 and 2000 cells/mm^2 exhibited the greatest decrease in cell density. In the current study, at 12 months postoperatively, cell density remained significantly and positively correlated with

preoperative CECD, despite a small positive correlation between preoperative CECD and mean cell loss. This suggests that where possible, it may be beneficial to plan for earlier cataract phacoemulsification surgery, as eyes will have a higher baseline CECD. Further studies to characterize this association would be beneficial.

Strengths of the present study include the use of routinely collected data and regular follow-up intervals in a contemporary cohort. All surgeries, preoperative measurements, and follow-up were conducted by the same ophthalmic surgeon, eliminating the impact of surgeon experience as a confounding factor.[9,12] Limitations of the present study include its retrospective nature. Other factors described to influence postoperative CECD, such as cataract grade,[1,2,7,12] infusion volume,[3,7] lens size,[7] and diabetes mellitus,[18,19] were unable to be evaluated, as were other markers of corneal endothelial integrity, such as cell size and morphology.[5,14] Prospective studies examining these variables and outcomes would provide more comprehensive information and improve predictability. Assessing the impact of longer ultrasound time and less power, compared to shorter ultrasound time, and more power is also an area of future research, as this could not be differentiated in the current study.

Conclusion

Significant corneal endothelial cell loss occurred over 3 years after cataract phacoemulsification surgery. The amount of cell loss increased with older age, preoperative CECD, and TOT. Planning for earlier surgical intervention and long-term monitoring of CECD may improve patient outcomes.

Data availability statement

The data that support the findings of this study are not publicly available. Data are, however, available from the authors on reasonable request.

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Nil.

Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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