Four-Year Survival of Descemet Membrane Endothelial Keratoplasty in Patients With Previous Glaucoma Surgery

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• PURPOSE: To evaluate 4-year outcomes of Descemet membrane endothelial keratoplasty (DMEK) in eyes with previous glaucoma surgery.
• DESIGN: Retrospective, comparative case series.
• METHODS: Patients with previous trabeculectomy or glaucoma drainage device (GDD) implantation who later underwent DMEK (study group) were matched for follow-up duration with Fuchs dystrophy DMEK patients (control group). The minimum follow-up was 18 months. Primary outcomes included graft survival and rejection rates, and secondary outcomes included rates of detachment/rebubble, endothelial cell loss, best spectacle-corrected visual acuity, intraocular pressure, and glaucoma medications/surgeries. Subgroup analysis compared eyes with and without a GDD.
• RESULTS: Ninety-four eyes of 91 patients were included. There were 51 eyes of 49 patients in the study group (GDD = 32 eyes, no GDD = 19 eyes) and 43 eyes of 42 patients in the control group. The mean follow-up was 37.9 ± 15.2 and 33.8 ± 13.5 months, respectively ($P = .322$). Graft survival probability of the study group at 12, 24, 36, and 48 months was 75%, 60%, 43%, and 27%, respectively, compared with a consistent 88% in the control group ($P < .001$). Survival curves of study subgroups (GDD and no GDD) were significantly lower than the control group ($P < .001$). Rejection rates in the study and control groups were 19.6% and 2.3%, respectively ($P = .010$). Endothelial cell loss in the study group was 12%-22% higher than the control group at 12, 24, 36, and 48 months ($P = .049$, $P = .027$, $P = .200$, and $P = .004$).
• CONCLUSIONS: In eyes with previous glaucoma surgery, DMEK has good early outcomes, but longer-term rejection and failure rates are high. Physicians and patients should be cognizant of the high likelihood of graft failure in this setting. (Am J Ophthalmol 2020;218: 7–16. © 2020 Elsevier Inc. All rights reserved.)

ENDOTHELIAL KERATOPLASTY HAS BECOME THE treatment of choice for corneal endothelial cell failure and continues to evolve as more data on surgical outcomes become available. Nevertheless, performing endothelial keratoplasty in some scenarios continues to be challenging. In eyes with a history of trabeculectomy or implantation of a glaucoma drainage device (GDD), adequate gas tamponade may be more difficult to achieve due to either active filtration of gas through the surgical glaucoma drain or posterior dislocation of gas through a large peripheral iridectomy. In addition, graft positioning and manipulation can be harder to perform due to either direct spatial interference created by a GDD or extensive synechiae.[1]

Published data show good short-term outcomes of Descemet membrane endothelial keratoplasty (DMEK) in the setting of previous glaucoma surgery,[2–4] albeit not as good as surgical outcomes in less complex eyes, such as those with Fuchs dystrophy.[5,6] In addition to lower visual outcomes of DMEK in eyes with previous glaucoma surgery, a possible trend toward increased rejection and secondary failure rates has been previously described.[2–4] Secondary failure in the setting of previous glaucoma surgery may be linked to either increased rejection rates or to direct endothelial cell loss caused by the presence of a GDD.[7] The risk of graft rejection and secondary failure is cumulative, and therefore longer-term follow-up is required to better understand survival of DMEK grafts in the setting of previous glaucoma surgery.

A recent study evaluating long-term outcomes of Descemet stripping endothelial keratoplasty (DSEK) in eyes with a GDD found that while DSEK was effective, graft survivability was only 50% at 3 years. To the best of our knowledge, published data on survival of DMEK grafts in the same setting are only available up to the second postoperative year. The purpose of this study was to evaluate 4-year outcomes of DMEK in eyes with previous glaucoma surgery, with an emphasis on 4-year graft survivability and rejection rates.

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METHODS

A RETROSPECTIVE CHART REVIEW WAS PERFORMED, including all eyes with a history of trabeculectomy or GDD implantation who later underwent DMEK between 2013 and 2017 at Toronto Western Hospital and the Kensington Eye Institute (Toronto, Ontario, Canada) and had ≥18 months of follow-up. Overall, 51 eyes of 49 patients with previous glaucoma surgery were included. Four-year survival as well as rejection, detachment, rebubble, and endothelial cell loss rates were compared with a control group consisting of eyes with Fuchs dystrophy that underwent simultaneous DMEK and cataract extraction by the same corneal surgeon (D.S.R.). This retrospective interventional case series received Research Ethics Board approval by the University Health Network (Toronto Western Hospital, Toronto, Ontario, Canada) and adhered to the tenets of the Declaration of Helsinki.

Sample size calculation was performed to determine the required control group size. Two-year survival probability of DMEK in eyes with previous glaucoma surgery (the longest available DMEK survival data in this setting) has been reported to be 67% by Birbal and associates.[3] Two-year DMEK survival rates of 91% have been previously reported by our group in patients with Fuchs dystrophy.[5] Assuming a statistical power of 80% and a significance level of $P = .05$, a control group size of 43 subjects was required, given the previously reported survival rates of 67% for the study group and 91% for the control group.[3,5] Pairwise matching using propensity score matching (caliper size = 0.25 standard deviations) was performed to match 43 eyes of 42 patients with Fuchs dystrophy who underwent DMEK (out of 95 available eyes). Matching was performed for follow-up time, given the importance of follow-up time for survival parameters.

• **SURGICAL TECHNIQUE:** All donor tissue used was stored in corneal storage solution (Optisol; Bausch & Lomb, Rochester, New York, USA) and received from the Eye Bank of Canada, Ontario division. The mean donor age was 66.8 ± 4.8 years. All procedures were performed by a single experienced corneal surgeon (D.S.R.) and were not among the first 50 DMEK surgeries performed by him. DMEK grafts were prepared as previously described.[8] Graft preparation was done according to the modified Melles technique using an "F" marking through a scleral window.[9]

Our DMEK technique has been described previously.[10] Briefly, descemetorhexis size was marked on the cornea, and 2 limbal paracenteses were performed at 2 and 10 o'clock. A temporal 2.4-mm clear corneal incision was performed. An anterior chamber maintainer was inserted inferotemporally into the anterior chamber. In previously vitrectomized eyes, a pars plana infusion was used to better control anterior chamber depth.[11] A descemetorhexis was created using a reverse Sinskey hook under balanced salt solution (BSS) infusion followed by removal of the recipient Descemet membrane. Vision Blue (D.O.R.C., Zuidland, Netherlands) was injected into the anterior chamber to ensure complete removal of Descemet membrane remnants. The 7 mm-9 mm donor Descemet membrane (size was chosen according to recipient white-to-white measurements) was loaded into either a glass pipet (Geuder AG, Heidelberg, Germany) or an intraocular lens injector (Monarch D, Alcon Labs Inc, Fort Worth, Texas, USA), and injected into the anterior chamber through the clear corneal incision. The anterior chamber infusion was turned on and off as needed to keep the anterior chamber shallow but was removed after injection of the donor tissue into the anterior chamber. The tapping technique was used to unfold and position the graft,[12] and the anterior chamber was then filled with air. BSS was injected into the anterior chamber, between the air bubble and the iris, to reduce the air bubble size up to a diameter slightly larger than that of the graft. No peripheral iridectomy was performed. Cyclopentolate hydrochloride 1% (MINIMS Cyc 1.0; Chauvin Pharmaceuticals Ltd, UK) and phenylephrine hydrochloride 2.5% (MINIMS PHNL 2.5; Chauvin Pharmaceuticals Ltd) were instilled to prevent pupillary block.

All patients remained supine for 2 hours and were then instructed to remain so as much as possible at home until the next morning. All patients were examined 2 hours and 1 day after surgery. Four patients required air release due to either elevated intraocular pressure (IOP) or a total anterior chamber air fill. All eyes underwent pressure patching overnight. The following day, 0.1% dexamethasone sodium phosphate and 0.3% tobramycin antibiotic (Tobradex; Alcon, Mississauga, Ontario, Canada) eye drops were administered 4 times daily for 1 week. Then, the antibiotic steroid drops were discontinued and 0.1% dexamethasone sodium phosphate (Maxidex; Alcon Labs Inc) eye drops were tapered down from 4 times daily to once daily over a 3-month period and continued once daily thereafter for a prolonged period of time. Hypotensive drops were maintained as preoperatively and changed according to clinical indication. Patients were examined at 1 week, 1 month, quarterly for the first postoperative year, semiannually for the second postoperative year, and annually thereafter.

Graft detachment was defined as any total or partial separation of the graft from the host cornea. Rebubbling was performed within 24 hours in eyes with Descemet membrane detachment of more than one-third of the DMEK graft area if no air bubble was left in the anterior chamber. Rebubbling was also performed 7-45 days postoperatively if there was unresolved Descemet membrane detachment that was causing persistent corneal edema either limiting rapid visual recovery or causing significant ocular surface discomfort. In cases of uncertainty, anterior segment optical coherence tomography (Optovue, Fremont, California,

USA) was performed to determine whether there was graft detachment. Primary graft failure was defined as persistent, nonclearing corneal edema 2 months after DMEK. Secondary graft failure was defined as corneal decompensation after an initially functional DMEK graft. Endothelial graft rejection was defined as the presence of inflammation as evidenced by anterior chamber cells, keratic precipitates or endothelial rejection line, or the presence of corneal edema with conjunctival injection and symptoms of pain or light sensitivity.

• **STUDY OUTCOMES:** Primary outcomes included graft survival and graft rejection rates. Secondary outcomes included rates of detachment/rebubble, visual acuity, endothelial cell loss, IOP, and glaucoma medications/surgeries.

• **DATA COLLECTION AND STATISTICAL ANALYSIS:** The data collected in this study included patient demographics, best spectacle-corrected visual acuity (BSCVA), associated operative procedures (including details on timing and indication for glaucoma surgeries), IOP, number of hypotensive ocular medications, intraoperative and postoperative complications, corneal donor characteristics, and endothelial cell density using a noncontact specular microscope (Robo, KSS 300; Konan Medical, Hyogo, Japan). In eyes where graft failure occurred, follow-up data were included up to the point of graft failure. Data after graft failure was not included in endothelial cell loss and BSCVA analyses. Data were also recorded on the management of failed grafts. In addition to comparison of the study group with a control group of patients with Fuchs dystrophy, a subgroup analysis within the study group compared survival, detachment, and rebubble rates between eyes that had a GDD (n = 32) and those that did not have a GDD (n = 19).

Data were recorded in Microsoft Excel 2016 (Microsoft Corp, Redmond, Washington, USA) and analyzed using the XLSTAT add-in (v 2019.1.2; Addinsoft, New York, New York, USA). Continuous paired variables were compared using the Wilcoxon nonparametric test. Continuous nonpaired variables were compared with the Mann-Whitney *U* test. Repeated measures analysis of variance and mixed effect models were used where appropriate. Categorical variables were analyzed using the Fisher exact test. Graft survival was analyzed using Kaplan-Meier survival analysis and was compared between groups using the log-rank test. All tests were 2-tailed, and the threshold for statistical significance was defined as a $P < .05$.

RESULTS

FIFTY-ONE EYES OF 49 PATIENTS (20 MEN AND 29 WOMEN) aged 68.0 ±16.1 years (range 26-94 years) were included in the study group. The mean follow-up time was 37.9 ± 15.2 months (range 18-66 months) in eyes with no failure and 24.1 ± 14.9 months (range 2-62 months) in eyes with failure. Forty-four eyes were pseudophakic, 3 eyes were phakic, and 4 eyes were aphakic. Thirty-two eyes had previous GDD implantation and 19 eyes had glaucoma surgery other than GDD implantation. Details on previous glaucoma procedures are shown in Table 1.

TABLE 1. Previous Glaucoma Procedures

Type of Glaucoma Surgery	Eyes, n
GDD	32
GDD only	24
GDD combined with trabeculectomy	7
GDD and a microshunt[a]	1
No GDD	19
Trabeculectomy only	18
Trabeculectomy and a microshunt[b]	1

GDD = glaucoma drainage device.
[a]Hydrus Microstent (Ivantis, Inc, Irvine, California, USA).
[b]Gold Micro Shunt (SOLX Inc, Waltham, Massachusetts, USA).

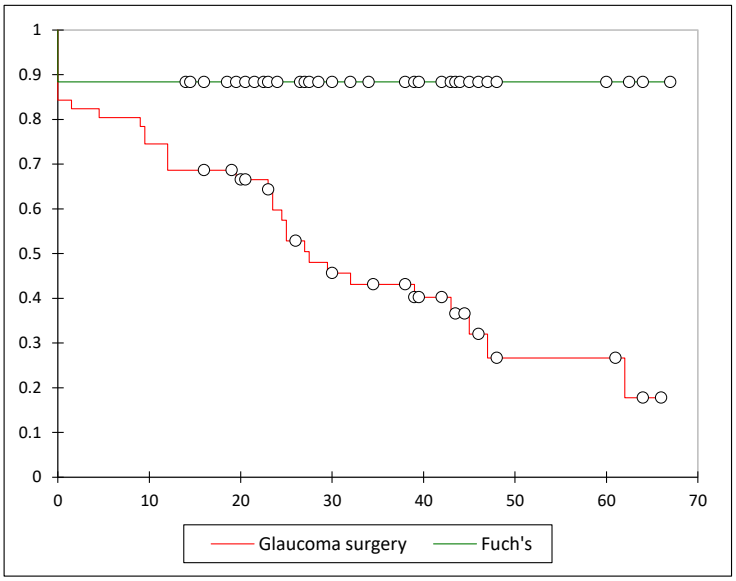
TABLE 2. Simultaneous Procedures Performed in Combination with Descemet Membrane Endothelial Keratoplasty (Study Group)

Procedure	Eyes, n
Tube trimming	8
Synechiolysis	6
Goniosynechiolysis	5
Posterior synechiolysis	1
Cataract extraction	3
Implantation of a scleral-fixated IOL (in aphakia)	2
IOL fixation (of a subluxed IOL)	2
Scleral fixation	1
Iris fixation	1

IOL = intraocular lens.

Indications for DMEK in the study group were pseudophakic bullous keratopathy (25 eyes), failed Descemet stripping endothelial keratoplasty (DSAEK; 12 eyes), failed penetrating keratoplasty (10 eyes), Fuchs endothelial dystrophy (3 eyes), and iridocorneal endothelial syndrome (1 eye). Details on additional surgical procedures that were combined with DMEK are shown in Table 2.

The control group included 43 eyes of 42 patients with Fuchs dystrophy (14 men and 28 women) aged 68.9 ± 9.2 years (range 48-89 years). The mean follow-up time of the control group was 33.8 ± 13.5 months (range 14-67 months, $P = .322$ compared with the study group). All eyes in the control group underwent DMEK combined with phacoemulsification and intraocular lens implantation.



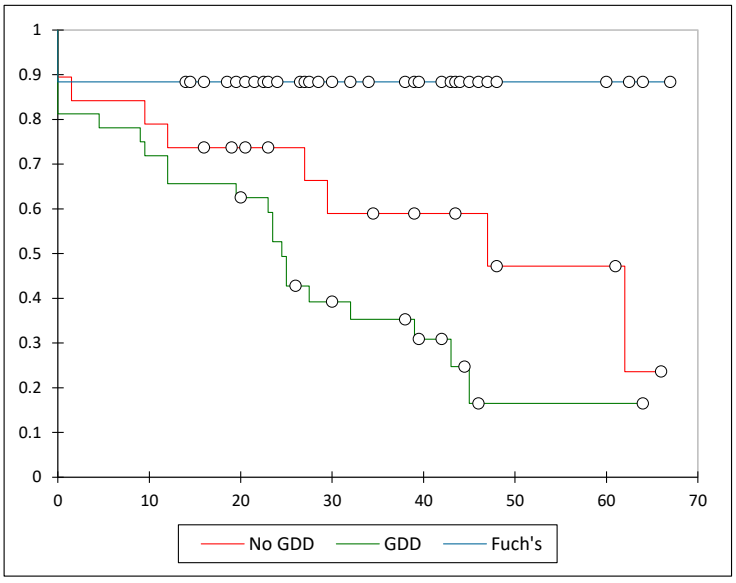
	Time (Months)	12	24	36	48	
Cumulative survival probability	**Fuch's dystrophy** (n at risk)	88% (43)	88% (28)	88% (17)	88% (6)	P<0.001
	Glaucoma Surgery (n at risk)	75% (40)	60% (28)	43% (17)	27% (6)	

FIGURE 1. Kaplan-Meier survival curve demonstrating the cumulative survival probability of Descemet membrane endothelial keratoplasty grafts in eyes with previous glaucoma surgery compared with Descemet membrane endothelial keratoplasty grafts in eyes with Fuchs dystrophy. Circles represent censored observations.

• **GRAFT SURVIVAL AND REJECTION:** Cumulative graft survival probability of the study group at 12, 24, 36, and 48 months was 75%, 60%, 43%, and 27%, respectively, and was significantly lower ($P < .001$) than a consistent survival probability of 88% in the Fuchs dystrophy (control) group (Figure 1). In the subgroup of study patients with a GDD (n = 32), cumulative survival probability was 72%, 53%, 35%, and 17%, respectively. In the subgroup of study patients with glaucoma surgery other than GDD (n = 19), cumulative survival probability was 79%, 74%, 56%, and 47%, respectively ($P = .08$ between the GDD and no GDD subgroups). Survival curves of the GDD group and the no GDD group were both significantly lower ($P < .001$) than that of the control group (Figure 2).

Primary and secondary failure in the study group occurred in 8 eyes (15.7%) and 24 eyes (47.1%), respectively. All primary failure cases were related to graft detachment except for 1 case that had persistent corneal edema despite an attached DMEK graft. All primary failures were managed with repeat surgery (5 with repeat DMEK, 1 with penetrating keratoplasty [PK], and 1 with DSAEK) except for 1 case where no further intervention was performed in accordance with the patient's request. The average time to secondary failure was 24.1 ± 14.9 months. Secondary failure occurred after graft rejection in 7 of 24 eyes, after a repeat trabeculectomy procedure in 1 of 24 eyes, after repair of an exposed GDD tube in 1 of 24 eyes, and after a corneal ulcer in 1 of 24 eyes. The remaining 14 of 24 eyes with secondary failures did not have a specific precipitating event. All secondary failures within the first postoperative year (5 cases) had a specific precipitating event (3 occurred after a rejection episode, 1 after a corneal ulcer, and 1 after repeat trabeculectomy). Management of secondary failure was surgical in 19 of 24 eyes (12 with repeat DMEK, 4 with PK, and 3 that are on surgery waitlist). In 5 of 24 eyes, no further intervention was done due to either poor visual potential (4 eyes) or in accordance with the patient's request (1 eye). Primary and secondary failure rates in the control group were 5 eyes (11.6%) and 0 eyes (0%), respectively. Primary failure rates did not differ significantly between the study and control groups ($P = .766$). The secondary failure rate was higher in the study group ($P < .001$).

Graft rejection in the study group occurred in 10 eyes (19.6%), at 8.8 ± 5.4 months, and was managed with high-dose topical steroids. Seven rejected grafts failed and 3 grafts recovered and remained viable at the last follow-up. In 7 of 10 eyes with rejection (70.0%), topical antirejection steroidal treatment was tapered down (either dose reduction or change to a less potent steroid) shortly



	Time (Months)	12	24	36	48	
Cumulative survival probability	**Fuch's dystrophy** (n at risk)	88% (43)	88% (28)	88% (17)	88% (6)	P<0.001
	GDD (n at risk)	72% (24)	53% (17)	35% (9)	17% (2)	
	No GDD (n at risk)	79% (16)	74% (11)	56% (8)	47% (4)	

FIGURE 2. Kaplan-Meier survival curve demonstrating the cumulative survival probability of Descemet membrane endothelial keratoplasty grafts in eyes with a glaucoma drainage device (GDD) and eyes with previous glaucoma surgery other than GDD compared with Descemet membrane endothelial keratoplasty grafts in eyes with Fuchs dystrophy. Circles represent censored observations.

before appearance of rejection symptoms. Graft rejection in the control group occurred in 1 eye (2.3%), a significantly lower rate compared with the study group (P = .010).

• **GRAFT DETACHMENT AND REBUBBLING:** Graft detachment occurred in 21 eyes (40.4%) in the study group and in 19 eyes (37.3%) in the control group (P = .836). Rebubbling was required in 12 eyes (23.5%) in the study group, and in 13 eyes (30.2%) in the control group (P = .491). Rebubbling was not performed in 5 study eyes whose detachment was not significant enough to require intervention and in 4 study eyes with total detachments that precluded rebubbling. Two of the 4 cases with total detachment occurred in DMEK grafts transplanted under a failed PK, 1 occurred in an aphakic eye that had combined DMEK and transscleral fixation of an intraocular lens (the DMEK graft in this case dislocated intraoperatively into the vitreous cavity through the aphakic orifice), and the fourth case had preoperatively a dislocated intraocular lens and underwent combined DMEK and iris fixation of the lens. In study eyes with a GDD (n = 32) and study eyes with glaucoma surgery other than GDD (n = 19), detachment occurred in 14 eyes (43.8%) and 7 eyes (36.8%), respectively (P = .771), and rebubbling was required in 8 eyes (25.0%) and 4 eyes (21.1%), respectively (P = 1.000).

• **VISUAL ACUITY:** Mean BSCVA improved significantly from 1.82 ± 0.88 logarithm of minimal angle of resolution (logMAR; Snellen equivalent ~20/1320) preoperatively to 1.06 ± 0.87 logMAR (Snellen equivalent ~20/230) at 6 months (P < .001), and remained significantly better than baseline at 12, 24, and 36 months (Figure 3). Mean BSCVA in eyes with no visual comorbidities (n = 26) improved significantly from 1.55 ± 0.80 logMAR (Snellen equivalent ~20/700) preoperatively to 0.49 ± 0.39 logMAR (Snellen equivalent ~20/60) at 6 months (P < .001), and remained significantly better than baseline at 12, 24, and 36 months (Figure 3). Mean BSCVA in eyes with visual comorbidities (n = 25) improved significantly from 2.11 ± 0.89 logMAR (Snellen equivalent ~20/2560) preoperatively to 1.62 ± 0.85 logMAR (Snellen equivalent ~20/825) at 6 months (P = .001), remained significantly better than baseline at 12 months, and was bordering significant difference from baseline at 24 and 36 months (Figure 3).

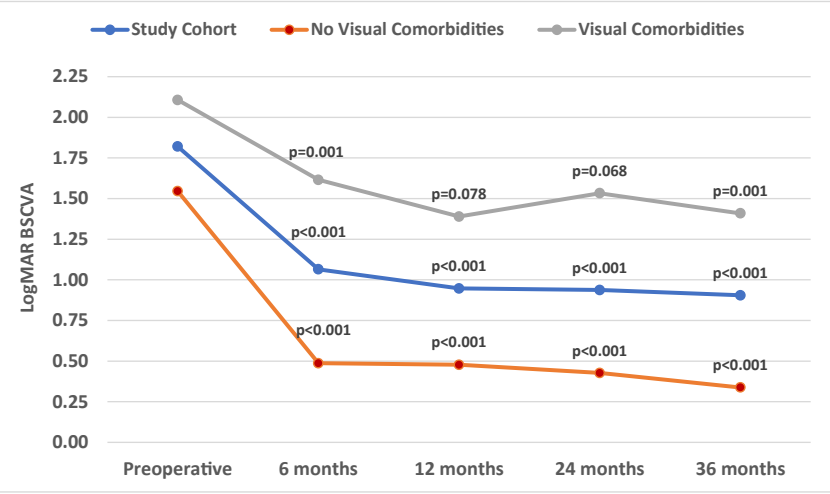


FIGURE 3. Mean logarithm of minimal angle of resolution (logMAR) best spectacle-corrected visual acuity (BSCVA) of the study cohort (n = 51) and of study eyes with visual comorbidities (n = 25) and without visual comorbidities (n = 26). *P* values were obtained using repeated measures analysis of variance and represent comparison with preoperative (baseline) examination.

• **ENDOTHELIAL CELL LOSS:** Mean donor endothelial cell densities of the study and control group were 2812 ± 244 cells/mm^2 and 2642 ± 192 cells/mm^2, respectively (P = .001). Cell loss rates of both groups were 44% and 35% at 6 months (P = .104), 48% and 35% at 12 months (P = .049), 54% and 41% at 24 months (P = .027), 59% and 47% at 36 months (P = .200), and 74% and 52% at 48 months (P = .004), respectively (Figure 4). The mixed effects model showed a general significant cell loss difference between the study and control groups (P = .039).

• **INTRAOCULAR PRESSURE:** Mean IOP (mm Hg) of the study cohort preoperatively and at 6, 12, 24, 36, and 48 months was 13.0 ± 5.2, 13.3 ± 6.5 (P = .524), 12.3 ± 5.2 (P = .904), 13.0 ± 6.8 (P = .965), 14.5 ± 6.6 (P = .233), and 12.1 ± 7.0 (P = .620), respectively. The mean number of hypotensive ocular medications used preoperatively and at 6, 12, 24, 36, and 48 months postoperatively was 1.7 ± 1.6, 1.6 ± 1.6 (P = .604), 1.5 ± 1.6 (P = .630), 1.4 ± 1.5 (P = .783) 1.4 ± 1.5 (P = .589), and 0.9 ± 1.5 (P = .564), respectively. Four eyes (7.8%) had IOP elevation during follow-up (IOP values 23-36 mm Hg). In 1 eye, IOP elevation was attributed to a failing bleb, and repeat trabeculectomy was performed 5 months after DMEK (DMEK graft had a secondary failure after repeat trabeculectomy). Three eyes were steroid responders—2 were managed successfully with the addition of 2 glaucoma medications and the third was already on maximal topical therapy and requested not to have any additional glaucoma interventions performed.

DISCUSSION

THIS STUDY EVALUATED 4-YEAR OUTCOMES OF DMEK IN eyes with previous glaucoma surgery. A handful of studies previously described good short-term outcomes of DMEK performed in this setting, with some suggesting a possible trend toward increased secondary failure and rejection.[2–4]

Aravena and associates[4] and Lin and associates[2] described early outcomes of DMEK in eyes with previous glaucoma surgery and found no secondary failures over the first postoperative year (with mean follow-up times of 9.7 and 11.6 months, respectively). Birbal and associates[3] described 2-year outcomes of DMEK in eyes with previous glaucoma surgery, showing that survival probability dropped from 89% at 1 year to 67% at 2 years (mean follow-up of 19.0 months). A similar survival drop was seen by Pasari and associates[13] in DMEK performed under a failed PK in eyes with previous glaucoma surgery, where 1-, 2-, and 3-year graft survival rates were 78%, 53%, and 39%, respectively (median follow-up of 21 months). Our current study shows that this trend carries over to the third and fourth postoperative years, with cumulative 2-, 3-, and 4-year DMEK survival probability rates of 60%, 43%, and 27%, respectively, in eyes with previous glaucoma surgery. Kang and associates[14] recently published long-term outcomes (mean follow-up of 36 months) of DSEK, performed in 85 eyes with a GDD, reporting a 3-year survival rate of 50%, which seems comparable to the 3-year DMEK survival rate found in our study. Anshu and associates[15] also evaluated 5-year DSEK survival in patients with preexisting glaucoma and found reduced survival rate in the subgroup of patients with previous glaucoma surgery (5-year graft survival rate of 52% in patients with previous trabeculectomy and 25% in patients with a GDD). In their study, previous glaucoma surgery was found to be a significant independent risk factor for DSEK graft failure. A similar drop in survival has also been reported in PK performed in this setting.[16–18] Reduced 4-year DMEK survival rates found in our study, together with previously

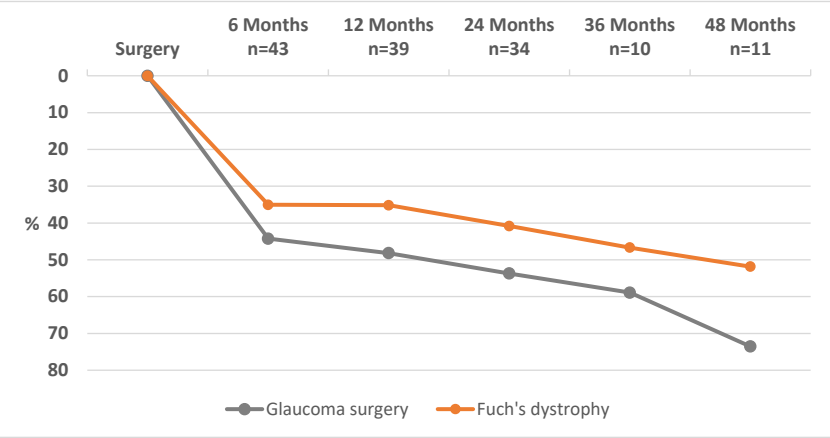


FIGURE 4. Endothelial cell loss rates after Descemet membrane endothelial keratoplasty in eyes with previous glaucoma surgery (study group) and in eyes with Fuchs dystrophy (control group). Eyes with failed grafts were not included in the analysis. The n value refers to the total number of eyes from both groups that had available endothelial cell counts at each timepoint.

reported long-term survival rates of DSEK and PK grafts in the same setting, signify that the inherent difficulty in those eyes persists in all types of corneal transplantation. Although we previously speculated that DMEK survival in this setting may be more favorable since it is thinner than a DSAEK graft and alters anterior chamber anatomy less than a PK graft, results of this study show otherwise. In fact, the 4-year DMEK survival rate of 27% found in our study group is lower than 4-year DSEK survival rate of 69% reported by Anshu and associates[15] in a similar setting. Although survival comparison of heterogenous groups between 2 published studies is not optimal, it does demonstrate the need for future studies directly comparing DMEK and DSAEK in this setting. In any case, proper patient counselling regarding DMEK graft survival prognosis in this setting is important, because patients should be aware that the likelihood of needing repeat transplantation within a few years is high.

The difference between survival curves of eyes with a GDD and those that had glaucoma surgery without a GDD was bordering significance ($P = .08$). When examining the 2 survival curves closely (GDD and no GDD; Figure 2), they appear to be parallel over the first postoperative year. Beyond the first year, survival of eyes with a GDD appears to decline more rapidly than that of eyes without a GDD. Secondary failures over the first postoperative year were all caused by acute events that significantly damaged the graft (3 occurred after a rejection episode, 1 after a corneal ulcer, and 1 after repeat trabeculectomy). Beyond that point, the role of ongoing endothelial cell loss probably became more dominant. The presence of a GDD has been shown to have a negative effect on the corneal endothelium,[7] while the presence of a filtering bleb should theoretically be less traumatic to the corneal endothelium compared with a GDD. This could explain survival differences found in the current study between eyes with a GDD and those that had no GDD. However, despite having better survival than eyes with a GDD, eyes without a GDD still had significantly reduced survival (2-, 3-, and 4-year survival probability rates of 74%, 56%, and 47%, respectively) compared with our control group ($P < .001$). This implies that additional factors other than the presence of a GDD affect long-term survival of DMEK grafts in patients with previous glaucoma surgery.

Rejection rate in our study group was high (19.6%) compared with the control group (2.3%, $P = .010$). Previous studies reported a similar trend toward increased DMEK rejection rate in eyes with previous glaucoma surgery. Lin and associates[2] had a rejection rate of 4% over 11.6 months of follow-up, while Birbal and associates[3] had a rejection rate of 9% over 19.0 months of follow-up, higher than rejection rates reported by their group in standard DMEK (0.2%-0.4%).[19] Given the inherent complexity of those eyes, it may be that their baseline inflammatory status is more active than expected due to factors such as an incomplete blood-aqueous barrier, making them more prone to immunologic rejection. In the current study, 70% of rejection cases occurred after a change in prophylactic topical steroids (either dose reduction or change to a less potent steroid). Steroidal treatment in glaucomatous patients is more problematic given their higher risk for steroid response and their reduced nerve fiber layer reserves.[20] Therefore, although the initial post-DMEK steroid taper is identical to non-glaucomatous patients, clinicians may have a lower threshold towards steroid dose reduction at a later stage in those patients. Steroid response rate in our study group was 7.8%, which does not seem higher than expected in glaucomatous and even nonglaucomatous eyes.[20] Mean IOP values as well as the number of glaucoma medications did not change significantly throughout follow-up. The high graft rejection rate and the relatively low steroid response rate found in

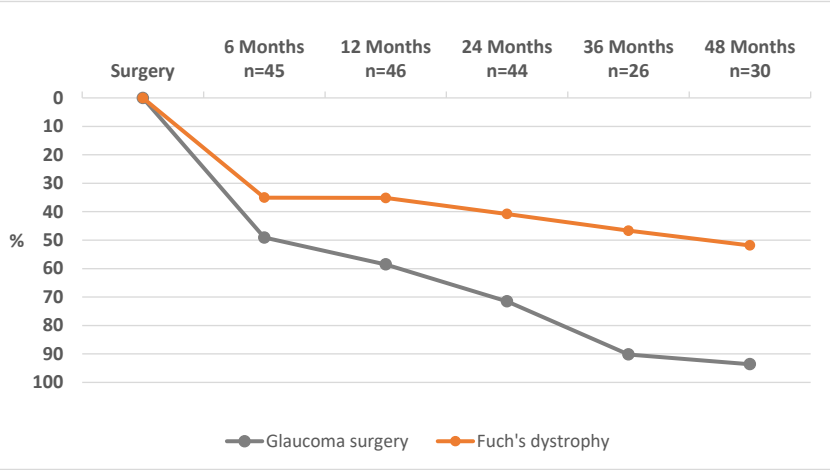


FIGURE 5. Endothelial cell loss rates after Descemet membrane endothelial keratoplasty in eyes with previous glaucoma surgery (study group) and in eyes with Fuchs dystrophy (control group). Grafts who had secondary failures were included in the analysis using a hypothetical cell loss value of 100% beyond the failure point. The n value refers to the total number of eyes from both groups that were included at each timepoint.

the study group raise the question of whether we should be more aggressive with our rejection prophylaxis regimen in this DMEK patient population then we initially thought, especially given the fact that 70% of the rejection episodes in the study occurred after steroid dose reduction. This important issue should be further investigated in future studies designed specifically for this purpose.

Endothelial cell loss was largest over the first 6 postoperative months (44%), mostly reflecting pretransplant injury and intraoperative and perioperative cell loss, with cell loss rates increasing thereafter at a steady rate of ~5% annually. Cell loss at 6 months after surgery was not significantly different than that of our control group (44% vs 35%; $P = .104$), indicating that perioperative cell loss was not substantially greater in surgically treated glaucoma eyes. Starting at 1 year after surgery, cell loss difference between the study and control groups increased to 12%- 22% throughout follow-up. Aravena and associates[4] found a similar trend in short-term follow-up of eyes with previous glaucoma surgery. They found no significant cell loss differences between eyes with previous glaucoma surgery and a control group during the early postoperative period, but at the last follow-up (mean follow-up 9.7 months), a significant cell loss difference (45% vs 33%) between the groups was seen. This reflects the higher ongoing cell loss that occurs in eyes with previous glaucoma surgery, as well as rejection-related cell loss and possibly additional mechanisms for cell loss in this setting. The aqueous environment is altered significantly after glaucoma filtration surgery, which could result in a more hostile environment for the corneal endothelium.[21] This could be a potential mechanism explaining the increased ongoing cell loss in those patients.

The consistently higher endothelial cell loss rate found in the study group may in fact be even higher. This is because failed grafts could not be included in cell loss analysis. Since failed grafts inherently suffer from the highest cell loss, and since there were more secondary graft failures in the study group, not being able to include them in the cell loss analysis would mean relative underestimation of cell loss rates in the study group. Figure 5 depicts cell loss rates with inclusion of grafts who had secondary failure (using a hypothetical cell loss value of 100% beyond the failure point) to demonstrate their potential effect on cell loss analysis.

Detachment and rebubble rates did not differ significantly between the control and study groups. In our subgroup comparison, detachment and rebubble rates also did not differ significantly between eyes with and without a GDD. Previous DMEK series in patients with trabeculectomy/GDD had comparable rebubbling rates of 22.0%-23.5%.[2–4] This is in contrast to what would be expected in patients with a filtering bleb or a GDD undergoing endothelial keratoplasty because attachment can be hampered by either mechanical interference of the GDD itself, difficulty obtaining and maintaining a good air fill because of active filtration of air through the ostium or tube, or posterior dislocation of air through a large iridectomy. Our findings suggest that eyes with a filtering bleb or a GDD that undergo DMEK do not have increased detachment and rebubble rates and need not have a more aggressive approach to air tamponade. This is in contrast with a high detachment rate (36.4%) reported by our group in DSAEK patients who had previous glaucoma surgery.[1] A study evaluating factors associated with graft detachment after primary DSAEK found previous trabeculectomy to be an independent risk factor for graft detachment.[22] A similar study in DMEK eyes found previous glaucoma surgery not to be significantly

associated with graft detachment.[23] The seemingly lower rebubbling rate in DMEK compared with DSAEK in eyes with previous glaucoma surgery may be explained by the fact that many of the patients with a trabeculectomy or a GDD have shallow chambers, where DMEK can be better manipulated than DSAEK. Also, obtaining a high-pressure air bubble is not as important in DMEK as in DSAEK, since in DMEK, the tissue is thin and has little mass. It should be noted that there were 4 total detachments in the study group (7.8%) which seems higher than would be expected in routine DMEK. However, in all 4 cases, factors predisposing to detachment such as a failed PK graft, aphakia, and an unstable lens–iris complex were present. Therefore, despite our above conclusion, we recommend considering measures for detachment prophylaxis (such as longer-acting tamponading gas, fuller gas fill, and more frequent follow-ups in the immediate postoperative period) in cases where additional factors predisposing to detachment exist. One study to date has compared rebubbling rates of DMEK and DSAEK in the setting of a GDD and found that although the rebubbling rates were 22% and 9%, respectively, this difference was not statistically significant. Additional head-to-head comparisons between DMEK and DSAEK in this setting could help us understand the advantages of each technique, as well as the specific scenarios where one technique should be chosen over the other.

This study has several limitations. First of which is its retrospective nature. In addition, because of high failure rates and missing observations, subgroup comparison of endothelial cell loss between eyes with and without a GDD was not possible and should be further evaluated in larger prospective series. Last, study group eyes were inherently more complex with variations in indications for DMEK, lens status, and simultaneous procedures performed. This may have had an effect on long-term DMEK outcomes in addition to the effect of previous glaucoma surgery. In particular, eyes with graft failure as an indication for DMEK may be at higher risk for rejection and subsequent failure. Nevertheless, this reflects a "real-world" clinical setting, where a large portion of DMEK eyes with previous glaucoma surgery have similar varying characteristics.

In conclusion, DMEK performed in eyes with previous glaucoma surgery has good early outcomes, but 4-year rejection and failure rates are high. Physicians and patients should be cognizant of the high likelihood of graft failure in this setting.

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