Advances in endothelial keratoplasty

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Chapter 4

Five-Year Graft Survival and Clinical Outcomes after Descemet Membrane Endothelial Keratoplasty: Results of the First 500 Consecutive Cases

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ABSTRACT

Purpose: To report the five-year graft survival and clinical outcomes after Descemet membrane endothelial keratoplasty (DMEK).

Methods: A retrospective, interventional case series was performed at a tertiary referral center. Five hundred eyes of 393 patients that underwent DMEK for Fuchs endothelial corneal dystrophy, bullous keratopathy, failed previous corneal transplants other than DMEK or other indications were evaluated for graft survival, best-corrected visual acuity (BCVA), endothelial cell density, postoperative complications, and retransplantation rate.

Results: Kaplan-Meier analysis demonstrated an estimated survival probability of 0.90 [95% Confidence Interval (CI), 0.87-0.94] for the entire cohort at 5 years after DMEK. At this time-point, 82% of the eyes achieved a BCVA of ≥20/25 (0.8), 54% achieved ≥20/20 (1.0) and 16% achieved ≥20/17 (1.2). BCVA continued to improve from 6 to 36 months after DMEK-surgery ($P \leq 0.005$) and then remained stable up to 60 months postoperatively ($P > 0.08$). Preoperative donor endothelial cell density averaged 2530 (±210) cells/mm^2 and decreased by 37% at 6 months, 40% at 1 year, and 55% at 5 years after DMEK-surgery ($P < 0.001$ between all follow-up time points). During the study period, allograft rejection episodes developed in 2.8% of the eyes, primary graft failure occurred in 0.2% and secondary graft failure in 2.8% of the eyes. Re-keratoplasty was required in 8.8% of the eyes.

Conclusions: Five-year graft survival after DMEK is high, and visual acuity outcomes remain excellent and are accompanied by a low longer-term complication rate.

INTRODUCTION

Descemet membrane endothelial keratoplasty (DMEK) has gained popularity worldwide and may become the gold standard in the management of corneal endothelial disorders.[1-3] By replacing only the diseased innermost corneal layers, this technique yields unprecedented visual outcomes with low complication rates.[4-8] As DMEK numbers increase globally, examining and reporting mid- and long-term outcomes of large cohorts becomes important and may help in refining the current technique and in determining expectations, especially in comparison with other keratoplasty techniques. However, so far, only few longer-term DMEK studies are available.[8-11]

We previously reported the 6- and 24-month clinical results of the first 500 consecutive eyes that underwent DMEK at our institute (excluding the very first 25 cases representing the technique learning curve).[6,7] The aim of the current study is to provide an overview of the extended clinical results of this cohort up to 5 years postoperatively, with a particlar focus on graft survival. Secondary to these analyses, we evaluated parameters that may influence outcomes after DMEK.

METHODS

Patient data

Five hundred consecutive eyes of 393 patients [mean age 68 (±12) years; range, 20-96 years] underwent DMEK for Fuchs endothelial corneal dystrophy (FECD; 89.2%), bullous keratopathy (BK; 6.4%), a failed previous corneal transplant other than DMEK (3.2%) or other indications (1.2%) (Table 1) and were retrospectively evaluated. The 500 cases evaluated were cases 26 to 525 from a total of 525 consecutive DMEK surgeries performed in our clinic between October 2007 and September 2012. The first 25 DMEK cases (cases 1-25), that represent the very first 25 DMEK cases performed worldwide and also the learning curve of this technique, were excluded from this study. Additional patient and donor demographics are reported in Table 1. All patients signed an institutional review board-approved informed consent form before surgery, and the study adhered to the tenets of the Declaration of Helsinki.

Table 1: Demographics Descemet membrane endothelial keratoplasty eyes and donors.

		(n)
Number of eyes/patients	500/393	(213/180)
Sex (female/male)	54%/46%	
Mean age (±SD) in years	68 (±12)	
Indication for DMEK		
FECD	89.2%	(446)
BK (pseudophakic, aphakic, phakic IOL)	6.4%	(32)
Failed PKP/DSEK/DSAEK/PLK	3.2%	(16)
Other (corneal dystrophies, BK due to congenital glaucoma, corneal decompensation due to trauma)	1.2%	(6)
Preoperative lens status		
Pseudophakic	74.8%	(374)
Phakic	24.8%	(124)
Aphakic	0.4%	(2)
Diabetes Mellitus	14.2%	(56)
Donor age (±SD) in years	65 (±10)	
Donor sex (female/male)	39%/61%	(194/306)
Donor death cause		
Cancer	25.2%	(126)
Cardiovascular/stroke	51.4%	(257)
Respiratory	16.2%	(81)
Trauma	2.4%	(12)
Other	4.8%	(24)
Total graft storage time in medium (±SD) in days	13.5 (±4)	

SD: Standard deviation
FECD: Fuchs endothelial corneal dystrophy
BK: Bullous keratopathy
PKP: Penetrating keratoplasty
DSAEK: Descemet stripping automated endothelial keratoplasty
DSEK: Descemet stripping endothelial keratoplasty
PLK: Posterior lamellar keratoplasty
DMEK: Descemet membrane endothelial keratoplasty

DMEK graft preparation and surgery

Donor tissue preparation at Amnitrans EyeBank Rotterdam was performed using the traditional and/ or standardized '*no-touch*' technique, as previously described.[12,13] Endothelial cell morphology and viability were evaluated before and after graft preparation. DMEK grafts were then stored in organ culture medium (CorneaMax; Eurobio, Courtaboeuf, France) until the time of transplantation; mean graft storage time was 13.5 (±4) days (Table 1).

DMEK surgery was performed based on the standardized '*no-touch*' DMEK technique in a single center, as reported before,[14] that is, the standardized technique was not implemented completely for the first 250 eyes of the study

group, whereas for the second 250 cases, it was fully applied.[6] The postoperative topical medication protocol consisted of chloramphenicol 0.5% 6 times daily for the first postoperative week tapered to twice daily for the second postoperative week and ketorolac tromethamine 0.4% and dexamethasone 0.1% 4 times daily for 4 weeks, which was switched to fluorometholone 0.1% 4 times daily at the 1- month visit. Flurorometholone was then gradually tapered to once daily at 9 months postoperatively. Twelve months after the DMEK, patients were advised to continue using fluorometholone once daily or every other day indefinitely.

Data collection and statistical analysis

Patients were evaluated preoperatively, at 6 and 12 months and then yearly, up to 5 years after DMEK. Central corneal thickness (CCT) was measured by rotating Scheimpflug corneal tomography (Pentacam HR, Oculus Optikgeräte GmbH, Wetzlar, Germany). Best-corrected visual acuity (BCVA) was assessed using a Snellen letter chart and is reported as best-spectacle-corrected visual acuity, except for 3 eyes at the 5-year follow-up for which only contact-lens corrected visual acuity was available. Endothelial cell density (ECD) was evaluated *in vivo* using a Topcon SP3000p non-contact autofocus specular microscope (Topcon Medical Europe BV, Capelle a/d IJssel, The Netherlands). For ECD counting, the commercial software of the specular microscope (ImageNet software, Topcon Medical Europe) was used and the automatically delineated cell borders were checked, and when incorrectly assigned, the cell borders were manually re-assigned by a trained technician. For each follow-up the results of 3 ECD measurements were averaged.

Outcome parameters (BCVA, ECD, CCT, postoperative complications, re-transplantation rate) are presented for all eyes with available follow-up data. The only exception was BCVA analysis, for which eyes with a low visual potential due to ocular co-morbidities unrelated to the cornea were excluded. The percentage of eyes with low visual potential did not exceed 11.8% of the study group at any included follow-up time point. BCVA outcomes were converted to the logarithm of the minimum angle of resolution (LogMAR) units for statistical analysis. When examining the influence of graft detachment, minor graft detachment was defined as a detachment ≤1/3 of the graft surface area and major graft detachment as a detachment >1/3 of the graft surface area. Allograft rejection was defined as the presence of an endothelial rejection line or keratic precipitates, with or without an increase in corneal thickness, anterior uveitis, and/ or ciliary injection on slit-lamp examination. Primary graft

failure (PGF) was defined as a cornea that failed to clear in the presence of an attached graft, while secondary graft failure (SGF) was defined as corneal decompensation after an initial period of a functional graft after DMEK.

Regarding statistical analysis, second eyes of patients undergoing bilateral DMEK (n=107) were excluded from the linear mixed model and survival analysis. Kaplan-Meier survival analysis was performed using SPSS 25.0 (SPSS Inc, Chicago, IL) to estimate the cumulative success probability of graft survival. All primary and secondary graft failures as well as retransplantations performed for graft detachment (technical failures)[15] were included as failures in the survival analysis. Log-rank tests were applied to test for equality of survival distributions of the different subgroups. Outliers were detected by visual inspection of histograms (baseline variables) and individual trajectories (outcomes). The influence of variables such as patient age, patient sex, lens status, surgery indication, graft storage time, intraoperative complications, graft adherence status, donor death cause, patient diabetes mellitus status, and donor age on ECD, BCVA and CCT was analyzed using linear mixed models with a random intercept and slope. *P* values were calculated using Wald tests. Mixed models were analyzed with package *lme4* using R version 3.5.0. All eyes were included for descriptive analysis, and analysis was performed using SPSS 25.0 and Excel Software for Windows.

RESULTS

Graft Survival

Kaplan-Meier survival analysis showed an estimated survival probability of 0.90 [95% CI, 0.87-0.94] for the entire cohort at 5 years after DMEK surgery (Table 2, Fig. 1).

The second group of 250 eyes undergoing DMEK surgery (0.94 [95% CI, 0.90-0.98]) showed a higher survival probability than the first group of 250 eyes undergoing DMEK surgery (0.88 [95% CI, 0.84-0.92]) ($P = 0.033$). Eyes operated on for FECD showed higher survival probabilities (0.93 [95% CI, 0.90-0.96]) than eyes treated for all other indications than FECD (0.72 [95% CI, 0.58-0.86]) ($P < 0.001$). Analysis based upon graft adherence status showed survival probabilities of 0.95 [95% CI, 0.93-0.98], 0.91 [95% CI, 0.81-1.01] and 0.27 [95% CI, 0.08-0.36] for fully attached grafts, grafts with a detachment of ≤1/3 of the graft surface area and graft with a detachment of >1/3 of the graft

Table 2. Cumulative Survival Probability after Descemet Membrane Endothelial Keratoplasty.

A - Total group	**Time (months)**		**0**	**6**	**12**	**24**	**36**	**48**	**60**
	Cumulative survival probability at FU	Estimate	.	0.98	0.95	0.94	0.92	0.91	0.90
		SE	.	0.01	0.01	0.01	0.02	0.02	0.02
	Cumulative events		0	9	19	24	30	33	34
	Remaining cases		393	375	355	327	297	276	250
B – First versus Second group of DMEK surgeries	**Time (months)**		**0**	**6**	**12**	**24**	**36**	**48**	**60**
1st Group	Cumulative survival probability at FU	Estimate	.	0.96	0.92	0.91	0.89	0.89	0.88
		SE	.	0.01	0.02	0.02	0.02	0.02	0.02
	Cumulative events		0	9	18	20	24	25	26
	Remaining cases		235	221	205	191	171	159	144
2nd Group	Cumulative survivals probability at FU	Estimate	.	.	0.99	0.97	0.96	0.94	0.94
		SE	.	.	0.01	0.01	0.02	0.02	0.02
	Cumulative events		0	0	1	4	6	8	8
	Remaining cases		158	154	150	136	126	117	106
C – Surgery indication (FECD vs. All other indications)	**Time (months)**		**0**	**6**	**12**	**24**	**36**	**48**	**60**
FECD	Cumulative survival probability at FU	Estimate	.	0.98	0.96	0.95	0.94	0.93	0.93
		SE	.	0.01	0.01	0.01	0.01	0.01	0.02
	Cumulative events		0	7	12	15	19	21	22
	Remaining cases		344	330	317	294	268	249	227
All other indication	Cumulative survival probability at FU	Estimate	.	0.96	0.85	0.80	0.75	0.72	0.72
		SE	.	0.03	0.05	0.06	0.07	0.07	0.07
	Cumulative events		0	2	7	9	11	12	12
	Remaining cases		49	45	38	33	29	27	23
D – Graft adherence status (Attached vs. Partially detached)	**Time (months)**		**0**	**6**	**12**	**24**	**36**	**48**	**60**
Attached	Cumulative survival probability at FU	Estimate	.	0.98	0.98	0.97	0.96	0.96	0.95
		SE	.	0.01	0.01	0.01	0.01	0.01	0.01
	Cumulative events		0	8	8	10	12	13	14
	Remaining cases		330	313	306	284	260	242	219
Detachment ≤1/3	Cumulative survival probability at FU	Estimate	.	.	0.97	0.94	0.91	0.91	0.91
		SE	.	.	0.03	0.04	0.05	0.05	0.05
	Cumulative events		0	0	1	2	3	3	3
	Remaining cases		38	38	35	32	29	28	26
Detachment >1/3	Cumulative survival probability at FU	Estimate	.	0.96	0.58	0.49	0.36	0.27	0.27
		SE	.	0.04	0.10	0.10	0.10	0.09	0.09
	Cumulative events		0	1	10	12	15	17	17
	Remaining cases		25	24	14	11	8	6	5

Cumulative graft survival probability is given for (A) the total study group and (B-D) divided into subgroups based on (B) first vs. the second group of surgeries; (C) surgery indication and (D) graft attachment status. In case of bilateral DMEK, only primary eyes were included for the survival analysis. (FU= follow-up, SE= standard error).

surface area [fully attached vs. ≤1/3 detached (P = 0.33); attached vs. >1/3 detached (P < 0.001), and ≤1/3 vs. >1/3 detached (P < 0.001)] (Fig. 1, Table 2).

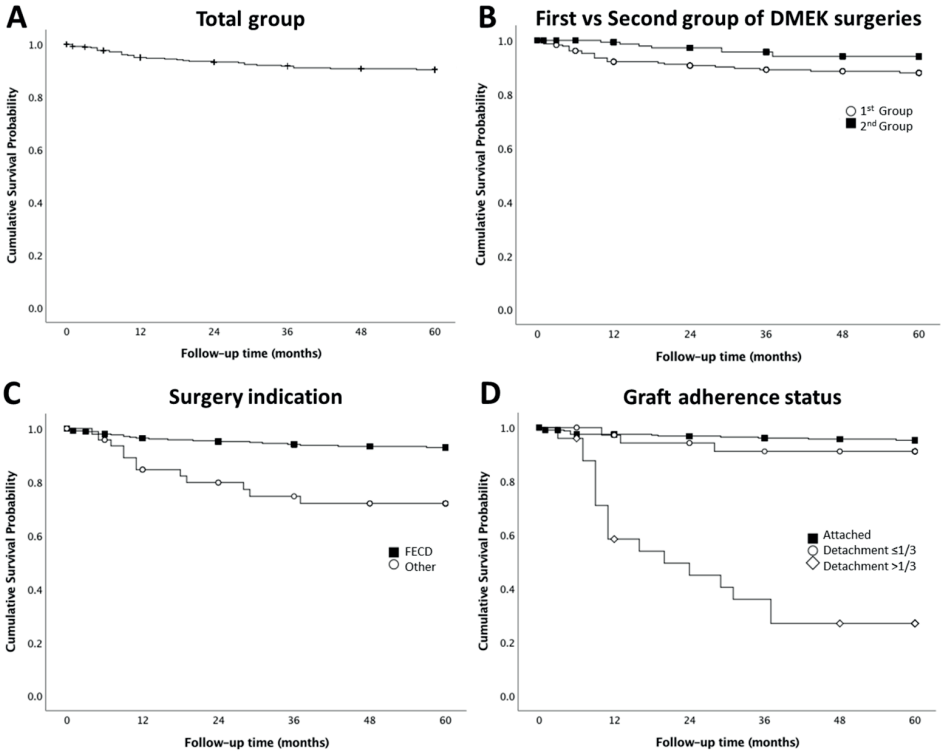

Figure 1. Kaplan-Meier curves showing the cumulative survival probabilities for Descemet membrane endothelial keratoplasty eyes.
Kaplan-Meier curves are shown for (A) the entire study group, (B) for the first 250 versus the second 250 operated Descemet membrane endothelial keratoplasty (DMEK) eyes, (C) for eyes operated on for FECD versus eyes operated on for all indications other than FECD, and (D) for eyes with completely attached grafts versus eyes with either a detachment of ≤1/3 of the graft surface area or eyes with a detachment of >1/3 of the graft surface area. Survival probabilities and number of eyes at risk per follow-up time-point are listed in Table 2.

Visual Outcome

At 5 years after DMEK, 82% of the eyes achieved a BCVA of ≥20/25 (0.8), 54% achieved ≥20/20 (1.0), and 16% achieved ≥20/17 (1.2) (Table 3, Fig. 2). BCVA improved from 6 to 36 months after DMEK surgery (P ≤ 0.005) and then remained stable up to 60 months postoperatively (P >0.08 for time).

Table 3. Best-corrected visual acuity, endothelial cell density, and pachymetry results after Descemet membrane endothelial keratoplasty.

Clinical outcomes	Preoperative	At 6-months follow-up	At 12-months follow-up	At 24-months follow-up	At 36-months follow-up	At 48-months follow-up	At 60-months follow-up
BCVA in Snellen (Decimal)	(n=451)	(n=418)	(n=396)	(n=360)	(n=329)	(n=306)	(n=278)
< 20/40 (< 0.5)	59.9%	6.0%	2.2%	1.6%	1.8%	1.6%	1.4%
≥ 20/40 (≥ 0.5)	40.1%	94.0%	97.8%	98.4%	98.2%	98.4%	98.6%
≥ 20/25 (≥ 0.8)	8.0%	75.1%	80.1%	81.6%	84.2%	81.8%	82.4%
≥ 20/20 (≥ 1.0)	1.3%	41.1%	48.3%	51.5%	52.3%	48.1%	53.6%
≥ 20/17 (≥ 1.2)	-	12.9%	14.7%	15.6%	18.2%	16.6%	15.5%
Mean BCVA (±SD), (logMAR)	0.49 (±0.39)	0.11 (±0.27)	0.06 (±0.15)	0.05 (±0.12)	0.05 (±0.13)	0.06 (±0.17)	0.05 (±0.12)
Endothelial cell density (ECD)	(n=456)	(n=447)	(n=427)	(n=392)	(n=360)	(n=334)	(n=303)
Mean ECD (±SD), (cells/mm^2)	2530 (±210)	1600 (±490)	1530 (±488)	1400 (±491)	1310 (±499)	1210 (±483)	1140 (±465)
ECD Decrease (±SD), (%)*		37 (±18)	40 (±18)	45 (±18)	49 (±18)	52 (±18)	55 (±17)
Central corneal thickness (CCT)	(n=425)	(n=428)	(n=423)	(n=378)	(n=351)	(n=327)	(n=297)
Mean CCT (±SD), (μm)	667 (±92)	525 (±46)	527 (±40)	534 (±43)	534 (±39)	537 (±43)	539 (±45)
CCT Decrease (±SD), (%)*		20 (±11)	20 (±10)	19 (±10)	20 (±10)	20 (±10)	19 (±10)

*Decrease as compared to preoperative values
BCVA: Best-corrected visual acuity
SD: Standard deviation

Parameters correlated with changes in visual acuity (in logMAR) up to 60 months after DMEK were surgical indication and graft attachment status ($P < 0.05$) (Table 4). Eyes with FECD as surgical indication achieved better visual acuity levels than eyes with other indications than FECD or BK, on average 0.11 on the logMAR scale ($P = 0.004$). Eyes with completely attached DMEK grafts attained better visual acuity outcomes than eyes with a partial graft detachment > 1/3 of the graft surface area, approximately 0.43 on the logMAR scale ($P < 0.001$). No significant difference in 5-year BCVA was observed for FECD versus BK eyes nor for eyes with completely attached grafts versus eyes with ≤ 1/3 graft detachment. These results were not affected when only eyes that had BCVA data at all follow-ups available were analyzed.

Table 4. Effects of the covariates from the linear mixed models on clinical outcome after Descemet membrane endothelial keratoplasty. Effects of covariates was analyzed for outcomes visual acuity (logMar), endothelial cell density and pachymetry for all eyes included in the statistical analysis (n=393).

	BCVA (logMAR)			**ECD ***			**Pachymetry**		
	Coeff.	SE	*P*-value	Coeff.	SE	*P*-value	Coeff.	SE	*P*-value
Intercept	-0.07	0.06	0.2656	2216.32	216.36	<0.0001	553.96	15.60	<0.0001
Patient Age (years)	0.00	0.00	0.0614	-4.57	2.47	0.0644	-0.38	0.21	0.0666
Sex (female vs. male)	0.02	0.02	0.3232	-56.41	43.80	0.1978	**-9.29**	**3.88**	**0.0166**
Lens status (phakic vs. pseudophakic)	-0.02	0.02	0.3135	**-127.41**	**63.07**	**0.0434**	-10.12	5.49	0.0654
Indication (BK vs. FECD)	-0.00	0.03	0.8888	**-293.76**	**93.87**	**0.0018**	7.02	8.32	0.3991
Indication ('other' vs. FECD)	**0.11**	**0.04**	**0.0042**	-120.92	118.64	0.3081	**55.41**	**17.80**	**0.0018**
Patient Diabetes mellitus (yes vs. no)	0.02	0.03	0.4820	42.83	72.66	0.5556	12.74	6.68	0.0566
Intraoperative complications (yes vs. no)	-0.03	0.02	0.2522	-74.85	64.06	0.2427	0.23	5.64	0.9668
Detachment (≤1/3 vs. attached)	0.03	0.03	0.3396	**-374.52**	**74.85**	**<0.0001**	6.21	6.54	0.3422
Detachment (>1/3 vs. attached)	**0.43**	**0.03**	**<0.0001**	**-291.78**	**114.66**	**0.0109**	**50.23**	**9.30**	**<0.0001**

BCVA:	Best-corrected visual acuity	Coeff.:	Regression coefficients fixed effects
ECD:	Endothelial cell density	SE:	Standard error
BK:	Bullous keratopathy	≤1/3:	Detachment of ≤1/3 of the graft surface area
FECD:	Fuchs endothelial corneal dystrophy		
'Other':	All surgery indications other than BK and FECD	>1/3:	Detachment of >1/3 of graft surface area

* For ECD, additional parameters including donor age (years), donor death cause (cancer vs. cardiovascular, respiratory vs. cardiovascular, trauma vs. cardiovascular, other vs. cardiovascular) and graft storage time (days) were evaluated. Of these parameters, only graft storage time (Coeff.=-12.09, SE=5.30, ***P*=0.0224**) was related to changes in ECD.
Bold numbers, statistically significant P values (P<0.05)

Endothelial cell density

Donor ECD averaged 2530 (±210) cells/mm^2 preoperatively and decreased to 1600 (±490) cells/mm^2 (-37%) at 6 months , 1530 (±488) cells/mm^2 (-40%) at 1 year, and 1140 (±465) cells/mm^2 (-55%) at 5 years after DMEK surgery (Table 3, Fig. 2). After the initial sharp decline in ECD observed in the first 6 months after DMEK, ECD values gradually continued to decrease. From 1 year after surgery, an annual ECD decrease rate of approximately 7% was observed. The ECD decrease was significant between all follow-up time points from 6 to 60 months after DMEK ($P < 0.001$).

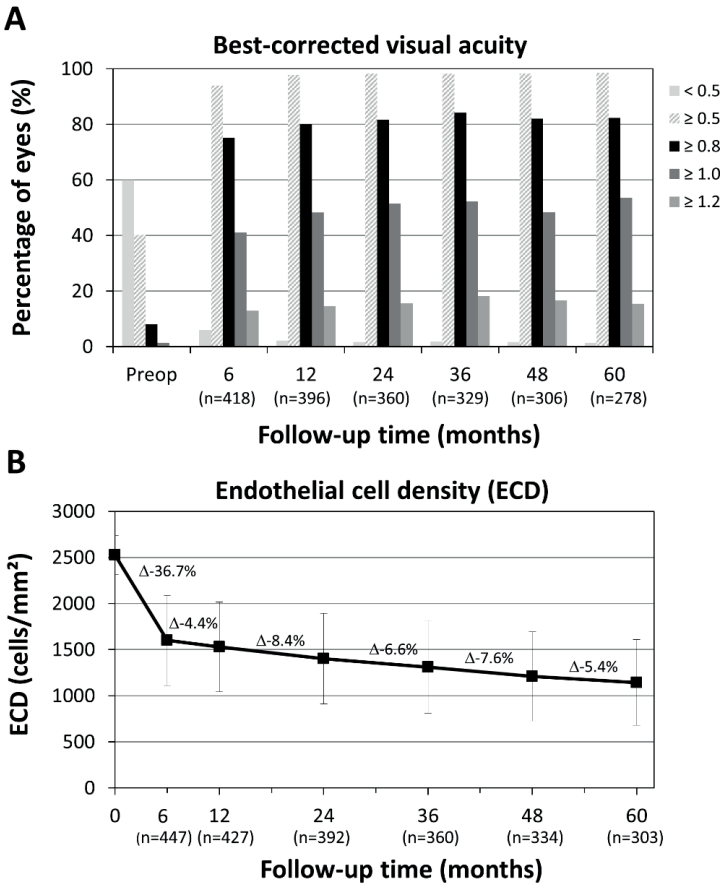

Figure 2. Graphs showing the best-corrected visual acuity and endothelial cell density outcome up to five years after Descemet membrane endothelial keratoplasty.
(A) Bar graphs displaying the percentage of eyes reaching best-corrected visual acuity (BCVA) levels (in decimal) as listed in the legend to the right. (B) Average endothelial cell density (ECD). Vertical bars represent standard deviations and percentages between follow-up time-points indicate the ECD decrease between these time-points.

Parameters associated with ECD outcomes included preoperative lens status, surgical indication, graft adherence status, and graft storage time (Table 4). Phakic recipient eyes had reduced ECD outcomes compared with pseudophakic recipient eyes (P = 0.04), and eyes operated on for BK had lower ECD outcomes compared with eyes operated on for FECD (P = 0.002). Analysis of graft adherence status revealed that eyes with completely attached DMEK grafts attained better ECD outcomes than eyes with a partial graft detachment ≤ 1/3 of the graft surface area (P < 0.001) or > 1/3 of the graft surface area (P = 0.01). Eyes receiving grafts with longer storage times had slightly reduced ECD outcomes compared with eyes receiving grafts within a shorter storage time (P = 0.02) (Table 4).

Pachymetry

Mean CCT improved from 667 (±92) µm before DMEK to 525 (±46) µm (-20%) at 6 months, 527 (±40) µm (-20%) at 1 year, and 539 (±45) µm (-19%) at 5 years after surgery (Table 3). Corneal thickness increased between 6 and 60 months after DMEK (P < 0.001). Parameters correlated with CCT outcomes included patient sex, surgery indication and graft attachment status (Table 4).

Postoperative complications and Retransplantation

A clinically proven allograft rejection episode occurred in 2.8% (n=14) of the entire study group during the 5-year study period. Two of these eyes (0.4%) developed allograft rejection after the patients had stopped using fluorometholone, and rejection was managed by restarting corticosteroids, whereas the other eyes (2.4%, n=12) developed rejection under corticosteroid use; of those, 1.6% (n=8) were successfully managed by applying an intensified corticosteroid regimen, while 0.8% (n=4) eventually required re-DMEK. Primary graft failure occurred in one eye (0.2%) and secondary graft failure in 2.8% (n=14) of the eyes, which included 4 eyes with a previous allograft rejection episode; 1.4% (n=7) of the eyes developed secondary graft failure within the first 2 years after surgery and the other 1.4% (n=7) after the second postoperative year. Out of 124 phakic DMEK eyes, 16.9% (n=21) underwent phacoemulsification cataract surgery within the study period.

Repeated keratoplasty was required in 8.8% (n=44) of all eyes [5.8% re-DMEK; 2.8% secondary DSEK; 0.2% secondary penetrating keratoplasty] and the majority of retransplantations were performed within 2 years after primary DMEK (6.4%, n=32). Indications for retransplantation included significant graft detachment (n=31), primary graft failure (n=1) and secondary graft failure (n=12).

Two eyes with a secondary graft failure did not undergo retransplantation within the study period.

DISCUSSION

The current study evaluated the 5-year graft survival and clinical outcomes of the first cohort to ever receive DMEK, excluding the initial learning curve cases, and also analyzed which parameters may influence these outcomes. Overall, our study confirms that DMEK continues to provide excellent clinical results up to 5 years postoperatively with high graft survival rates, in particular for eyes operated on for FECD and after technique standardization.

With an overall 90% cumulative graft survival rate achieved at 5 years after DMEK, our DMEK cohort had a slightly lower graft survival probability than the previously reported 93% and 96% DMEK graft survival rates.[8,10] This slight discrepancy may be on the one hand due to the fact that one of the previous studies only included FECD eyes,[10] that tend to have better survival probabilities than eyes with other surgery indications (as shown for our cohort here, with a 93% survival rate for FECD eyes only vs. 72% for other indications). On the other hand, because this is the first DMEK cohort ever, it is important to realize that these results still include a technique learning curve effect, even after excluding the very first 25 DMEK cases, which is reflected by the higher survival probability for the second 250 DMEK cases versus the first 250 cases (88% vs. 94%). This learning curve effect is also reflected by the fact that most eyes with a graft detachment of >1/3 of the graft surface area are part of the first 250 eyes (4.4% vs. 2.4%).[6] For these eyes, significantly lower survival probabilities were observed than for eyes with completely attached grafts or only small detachments, corroborating the beneficial effect of an early re-bubbling procedure. While in the first years after introducing DMEK, we often avoided performing a re-bubbling procedure in eyes with a partial graft detachment, as some corneas may show spontaneous corneal clearance or graft attachment, we nowadays usually await the 1-week follow-up before deciding for a repeat air injection,[16] and perform the procedure at its latest 6 to 8 weeks after DMEK.[17]

When comparing DMEK graft survival rates with those reported for Descemet stripping automated endothelial keratoplasty (DSAEK/DSEK) and penetrating keratoplasty (PK), which vary from 76 to 97%[18-23] and 67 to 93%,[21,24] re-

spectively, DMEK has demonstrated to provide at least similar survival rates. When hypothesizing that improved outcomes may be attributed to technique standardization and increased surgical experience, DMEK may surpass graft survival of DSAEK/DSEK and PK in the longer term.

In regard to BCVA, this study confirms that the excellent visual outcomes achieved at 6 months after DMEK are maintained until at least 5 years postoperatively. In contrast to our previous results,[7,9] continued BCVA improvement was observed from 6 to 36 months postoperatively. This may be attributed to a selection bias, as especially the elderly patients, who tend to have lower BCVA outcomes, are withdrawing from continuous follow-up, whereas younger patients are more consistently attending follow-up visits. Furthermore, unlike the 2-year BCVA results, 5-year BCVA results did not differ between FECD and BK eyes and also not between eyes with a completely attached graft and eyes with a ≤1/3 graft detachment.[7]

At 5 years after DMEK, ECD had decreased by approximately 55%, of which the main decrease was observed within the first 6 months after surgery. ECD decrease showed a similar course as after DSAEK/DSEK,[19-21,23] but a slower and more favorable decrease when compared with after PK.[25,26] With longer follow-up data for larger study groups, available in the near future, it will be interesting to analyze whether ECD will decrease linearly or exponentially and how this may impact long-term graft survival. Similar to our previous studies, main parameters associated with 5-year ECD outcomes included preoperative lens status, surgery indication, and graft adherence.[6,7]

The overall postoperative complication rate remained relatively low throughout the study period. As reported previously, partial graft detachment was the main early postoperative complication, whereas allograft rejection and secondary graft failure constituted the more severe complications in the later postoperative period.[6,7] With longer follow-up times available, the cumulative allograft rejection rate after DMEK now exceeds the initially reported rejection rate of approximately 1%, but is still lower than 5-year rates reported for DSAEK/DSEK and PK, 5.0 to 7.9%[18,21]and 14.1%,[21] respectively. In a recent study, Price et al. showed that even though rejection episodes were associated with increased ECD loss, they were not a risk factor for graft failure. The latter may be due to the fact that allograft rejection episodes after DMEK tend to be milder than with the other forms of keratoplasty and can usually be managed with an intensified corticosteroid regimen. Secondary graft failure occurred in

a similar percentage as reported for other DMEK studies[8] but in a lower rate than after DSAEK/DSEK and PK.[18-20,23,22,27] With an average annual graft failure rate of approximately 0.5% after the second postoperative year, failure rates after DMEK remain low up to the 5-year follow-up. For future longer-term studies, it will be important to see how these rates evolve, particularly when eyes approach the 500 cell/mm^2 ECD threshold.

Limitations of this study include the retrospective nature of the study and the increasing number of patients being lost to follow-up at longer follow-up time-points. However, when comparing our study with other DMEK studies with 5-year follow-up, we can still include a relatively high number of eyes at each follow-up time-point.[8,10,28]

In conclusion, DMEK yields favorable graft survival rates and provides fast and near-complete visual rehabilitation that is maintained up to at least 5 years postoperatively and that is accompanied by a low complication and retransplantation rate.

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