Graft Survival and Clinical Outcomes of Descemet Membrane Endothelial Keratoplasty: Long Term Results

NILAY KANDEMİR BESEK (✉ kandemirnilay@hotmail.com)

Prof. Dr. N Resat Belger Beyoglu Goz Egitim ve Arastirma Hastanesi <https://orcid.org/0000-0002-5784-9895>

Glay Yalinkaya

Beyoglu Eye Training and Research Hospital: Prof Dr N Resat Belger Beyoglu Goz Egitim ve Arastirma Hastanesi

Ahmet Krgz

Beyoglu Eye Training and Research Hospital: Prof Dr N Resat Belger Beyoglu Goz Egitim ve Arastirma Hastanesi

Semih akmak

Beyoglu Eye Training and Research Hospital: Prof Dr N Resat Belger Beyoglu Goz Egitim ve Arastirma Hastanesi

Selim Gen

Beyoglu Eye Training and Research Hospital: Prof Dr N Resat Belger Beyoglu Goz Egitim ve Arastirma Hastanesi

enay Aık Nacaroglu

Beyoglu Eye Training and Research Hospital: Prof Dr N Resat Belger Beyoglu Goz Egitim ve Arastirma Hastanesi

Burin Kepez Yıldız

Beyoglu Eye Training and Research Hospital: Prof Dr N Resat Belger Beyoglu Goz Egitim ve Arastirma Hastanesi

Yusuf Yildn

Beyoglu Eye Training and Research Hospital: Prof Dr N Resat Belger Beyoglu Goz Egitim ve Arastirma Hastanesi

Alper Aca

Beyoglu Eye Training and Research Hospital: Prof Dr N Resat Belger Beyoglu Goz Egitim ve Arastirma Hastanesi

Keywords: Ocular Surface Surgery, Corneal Dystrophies, Corneal Degenerations, Corneal Transplantation, Diseases of the Ocular Surface

Posted Date: August 4th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-263813/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Purpose: The aim is to report long-term graft survival rates, clinical outcomes of Descemet membrane endothelial keratoplasty (DMEK).

Methods: In this study 150 eyes, that underwent DMEK whether for Fuchs endothelial corneal dystrophy (FECD) or for bullous keratopathy (BK), surveilled for 7 years at 6 time-points to evaluate graft survival rates and clinical outcomes of post-corneal transplantation.

Results: Overall, the estimated survival probability of 95% confidence interval at 7 years of post-DMEK was 0.58 (0.72-0.77) and the survival probabilities of eyes operated for FECD (0.53) were higher than eyes operated for BK (0.42) (Log Rank 26.87, [$p=0.197$]). Post-transplant eyes with FECD achieved better visual acuity levels than eyes with BK ($p=0.006$). Primary graft failure occurred in 11.3% eyes. Secondary graft failure rate was 9.3%, and allograft rejection rate was 4.7%.

Conclusion: Although DMEK is effective, safe in long-term, visual results and graft survival rates are better in cases with FECD.

Introduction

Melles introduced Descemet membrane endothelial keratoplasty (DMEK) for patients with corneal endothelial dysfunctions for the first time in 2006 [1]. Since then, it has become a preferable therapy with expedited visual recovery, and better refractive and ocular-surface integrity results [2,3]. Compared to penetrating keratoplasty (PK), DMEK is a minimally invasive surgery and provides better anatomic restoration of the corneal surfaces than Descemet stripping endothelial keratoplasty (DSEK), which is another type of lamellar endothelial keratoplasty [4,5].

One of the disadvantages of DMEK is probability of corneal damage during removal of the graft from the donor, where loss of endothelial tissue is possible [6,7]. In addition, during the surgery, there might be difficulty in obtaining the graft from an incision in the anterior chamber, which leads to greater tissue manipulation, resulting in damaged endothelial cells and increased graft detachment [8-10]. However, assessment of the learning curve for graft preparation and implantation could reduce the complications of DMEK and enhance the success of the procedure by establishing a good standard of care[11].

There are plenty of short-term clinical outcomes reported for the transplantation in the literature [5], but there are limited data from long-term post-surgery follow-up. One recent example is the study by Vasiliauskaitė *et al.* [12], who suggested that the 10-year graft survival rate is 0.79. Therefore, in the present study, we aimed to evaluate the long-term clinical outcomes and graft survival rates of a group of post-DMEK cases.

Materials And Methods

Study design, patient selection, and data collection

Between 2013 and 2019, 137 consecutive patients underwent DMEK for Fuchs endothelial corneal dystrophy ([FECD], 61 eyes, 40.7%) and bullous keratopathy ([BK], 89 eyes, 59.3%). In total, 150 eyes of such patients were operated on (Table 1) and evaluated retrospectively. The present study was performed in conformance with the principles of the Declaration of Helsinki after obtaining approval from the Local Ethics Committee of Okmeydani Training and Research Hospital, Istanbul, Turkey. Written informed consent was also obtained from all patients before the procedure.

Patients were excluded from the study if they had conditions that might affect their vision, such as retinal detachment, recurrent uveitis, trauma, proliferative diabetic retinopathy, macular holes, glaucoma, retinal vascular occlusion, age-related macular degeneration etc. Eyes were also excluded if they had less than 6 months of follow-up. This mono-centre study also included three surgeons' learning curves and early adoption techniques for the standardization of the implantation. The data recorded during the study period included preoperative demographic and medical data (sex, age at date of visit, surgical indications, lens situation, visual acuity), intraoperative data (number of donor endothelial cells, graft size, complications), and postoperative data (best corrected visual acuity [BCVA], endothelial cell density [ECD], presence of graft/detachment of graft, primary and secondary graft failure, and other postoperative complications).

Corneal allograft rejection was defined as an endothelial rejection line or inflammation with keratic precipitates, cells in the stroma, or an increase in aqueous cells from a previous visit, with or without any clinically apparent change in recipient stromal thickness or clarity [13].

Based on the study by Lass *et al.* [13], graft failures were classified as primary graft failure (PGF) if the graft was cloudy on the first postoperative day and did not clear up or if it required a re-graft within 8 weeks. Secondary graft failure (SGF) was considered to occur when the cornea was initially clear but later became cloudy in 3 months.

A Snellen letter chart was employed to evaluate BCVA. For statistical analyses, the visual acuity measurements were converted into logMAR values. Preoperative number of donor endothelial cells were obtained from the Beyoglu Eye Bank donor documentation as counted with a specular microscope (Cell Check, Konan Medical Inc, USA). Patients' endothelial cell density (ECD) was visualized under a non-contact auto-focus Nidek Cem-530 specular microscope (Nidek CO., Gamagori, Japan) at 6 months and the 1st, 3rd, 5th, and 7th years post-surgery. Furthermore, central corneal thickness (CCT) was measured with Sirius corneal topography (Costruzione Strumenti Oftalmici, Italy), and graft-attachment/detachment was evaluated by anterior segment optical coherence tomography (OCT) (Carl Zeiss Meditec. Inc., Dublin, USA).

Surgical procedure

For all DMEK procedures, grafts were obtained from donor globes within less than 36 hours post mortem. From the ocular globes, corneo-scleral buttons were excised, and the organ culture was stored in modified minimum essential medium (EMEM) at 31°C [14]. The average donor age was 53.34 ± 12.75 years, and the donors' average endothelial cell count was 2572 ± 250 cells/mm² until the time of transplantation. The mean graft storage time was 10.58 ± 1.92 days (Table 1).

The Beyoglu Eye Training and Research Hospital Cornea Bank provided us with all corneas, and before the surgery, Descemet membranes (DMs) were separated from the donor corneas with a 360° manual dissection. DMs were detached and cut using a 7.75-mm punch. Immediately after, they were stained with trypan blue dye (0.06%). A single peripheral triangular mark was made with a micro-scissor, and the DM was completely separated from the donor cornea [15]. Finally, they were re-stained with trypan blue dye and stored in EMEM solution until the day of DMEK.

We performed a similar surgical technique to the one developed by Melles *et al.* [1]. Briefly, under sub-tenon's anaesthesia, 3 side-port incisions were created in the superotemporal, superonasal, and inferotemporal quadrants, respectively. Right after administering 0.01% carbachol (Miostat; Alcon Laboratories Inc.) to the anterior chamber, a peripheral iridectomy was performed through a vitrectomy. After filling the anterior chamber with air (35 mmHg), descemetorhexis was performed, and the host DM was removed.

We assembled a device with an Alcon Monarch C cartridge, along with serum set. After entering the temporal quadrant with a 2.75-mm scalpel as the main incision of the procedure, the DM was taken into the cartridge using the injector's negative pressure, and the donor's DM was placed in the anterior chamber through the main incision using the cartridge once more. The anterior chamber and side incisions were flattened, and a tapping technique was used to unfold and position the graft. As a tamponade, an air bubble or sulphur hexafluoride (SF₆-gas) was injected underneath the graft to position it against the recipient's posterior stroma, and then the main incision was closed up with 10/0 nylon suture. In all phakic cases, standard phacoemulsification and intraocular lens implantation were performed prior to DMEK surgery.

All patients were kept strictly in a supine position throughout the first 24 hours after the surgery. Postoperatively, dexamethasone (0.1%, 4x/day) was administered for 4 weeks and then changed to fluorometholone (0.1%, 4x/day) at the 1st-month visit, which was gradually decreased to once a day at the 12-month visit. Additionally, topical antibiotics were prescribed for approximately 2 weeks along with lubricant eyes drops (5 times a day).

At the first day post-operation, all recipients' anterior segment underwent OCT imaging to see whether the graft was properly attached. If the DM was more than 1/3 detached, the eyes were re-bubbled in 24-36 h. If the DM was less than 1/3 detached and there was cornea edema, patients were followed-up for 2-3 weeks. When edema was persistent, re-bubbling was injected. In cases of graft failure, DMEK was repeated or PK was performed.

Statistical analyses

A descriptive analysis was carried out for all eyes using SPSS 17.0 (SPSS Inc., Chicago, IL). Kaplan-Meier survival analysis was performed to estimate the cumulative success probability of graft survival. All primary and secondary graft failures and re-transplantations were considered as failures in the survival analysis. Log-rank tests were used to compare the survival time distributions of different subgroups. Linear mixed models with a random intercept were used for the analysis of the influence of parameters such as the patients' age, sex, lens status, surgery indication, graft storage time, adherence status, donors' cause of death, and age on BCVA, ECD, and CCT. Analyses were repeated for tests comparing groups at multiple time points, and p -values were Bonferroni adjusted ($p < 0.01$).

Results

In this retrospective study, 150 eyes of 137 patients were evaluated (males: 66 [43.7%]; females: 84 [55.6%]). The patients' mean age was 65.9 ± 12.86 years and ranged from 24 to 89 years. Patients' and donors' demographics and clinical data were recorded, as shown in Table 1. Patients were followed-up at 6th months and the 1st, 3rd, 5th, and 7th years post-DMEK (148, 146, 82, 38, and 20 patients, respectively). The mean time of surveillance was 36.71 ± 22.69 months.

Graft survival

For the entire cohort, the Kaplan-Meier survival analysis indicated that the estimated survival probability of seven years of post-DMEK surgery was 0.58 (95% confidence interval [CI], 0.72 - 0.77; Table 2; Figure 1). Eyes treated for FECD had higher survival probabilities (0.53 [95% CI, 0.60-0.71]) than eyes operated on for BK; however, this was not statistically significant (0.42 [95% CI, 0.51-0.64]; Log Rank 26.87, [$p=0.197$]) (Figure 2). The analysis based on graft adherence status indicated that survival probabilities were 0.48 (95% CI, [0.63-0.72] and 0.10 (95% CI, 0.34–0.52) for fully attached grafts and grafts with a detachment, respectively (minor: $\leq 1/3$ of the graft surface area; major: $>1/3$ graft surface area; Log Rank 26.87, $p \ll 0.001$).

Endothelial cell density (ECD)

Preoperatively, the patients' mean ECD was 2572 ± 250 cells/mm², while postoperatively, it decreased gradually to 1793 ± 636 cells/mm² at the 6th month, 1688 ± 626 cells/mm² at the 1st year, 1532 ± 608 cells/mm² at the 3rd year, 1310 ± 525 cells/mm² at the 5th year, and 1190 ± 441 cells/mm² at the 7th year. ECD declined by 37% (± 20.75), 42.58% (± 19.04), 44.75% (± 17.83), 47.49% (± 13.60), and 55.03% (± 13.41), respectively, compared to preoperative ECD values (Table 3). The decrease in ECD was significant at all visits from 6 months to the 5th year post-DMEK ($p \ll 0.001$). When the mean ECD between 5th-7th years was compared, it was statistically significantly lower in 7th year ($p=0.01$). Although there was a negative correlation between ECD and graft storage time, it was not statistically significant ($p=0.091$), and no correlation was found between donor age, cause of death, and ECD ($p \gg 0.05$). Female patients had a positive correlation with ECD ($p=0.035$), and there was a negative

correlation between patients' age and ECD ($p=0.034$). There was also a negative relationship between eyes with minor ($p=0.031$) and major ($p=0.01$) detachment and ECD values (Table 4), but no statistically significant differences were found with eyes that underwent re-bubbling and those that did not, and ECD declined over the years ($p=0.05$).

Best corrected visual acuity (BCVA)

The outcomes of BCVA post-DMEK were 0.73 ± 0.51 at the 6th month, 0.51 ± 0.45 at the 1st year, 0.38 ± 0.26 at the 3rd year, 0.44 ± 0.23 at the 5th year, and 0.38 ± 0.25 at the 7th year control ($p=0.01$; Table 3). According to the Snellen letter chart measurement, the mean improvement in visual acuity was 0.31 ± 0.25 in a year. However, despite preoperative BCVA (logMAR) scores being high, in the 6 month and beyond, follow-up measurements showed no significant improvement in visual acuity ($p>0.05$). BCVA between 1st and 7th years postoperatively were statistically similar (postoperative 6th month-1st year $p=0.067$, 1st-3rd years $p=1.00$, 3rd-5th years $p=1.00$ and 5th-7th years $p=1.00$, respectively after Bonferroni adjusted).

Eyes with FECD attained better visual acuity levels than eyes with BK with an average of 0.18 on the logMAR scale ($p = 0.006$). There was a correlation between visual acuity at 7 years and age, and older recipients had better logMAR scores ($p=0.009$; Table 4). No correlation was found between major and minor detachments and 7-year logMAR measurements (Table 4). Furthermore, there was no correlation between donor age and cause of death, graft storage time, and BCVA logMAR scores ($p > 0.05$). There were no significant differences between logMAR measurements of cases that underwent re-bubbling and those that did not ($p=0.316$).

Corneal pachymetry

The mean CCT in preoperative eyes was $665 \pm 126 \mu\text{m}$, and the mean CCT in postoperative eyes was $568 \pm 102 \mu\text{m}$ at the 6th month, $572 \pm 93 \mu\text{m}$ at the 1st year, $572 \pm 91 \mu\text{m}$ at the 3rd year, $575 \pm 94 \mu\text{m}$ at the 5th year, and $578 \pm 54 \mu\text{m}$ at the 7th year (Table 3). Changes in corneal thickness were statistically significant between preoperative and postoperative measurements for the 6th month ($p<0.01$), while the other repeated measures were similar ($p>0.05$). There was a negative correlation between ECD and pachymetry results ($r= -0.04$, $p=0.036$), but pachymetry had a positive correlation with graft storage time ($r=15.48$, $p=0.008$). No association was found of CCT outcomes with patients' age, sex, lens status, indication of DMEK, and status of graft attachment (Table 4).

Postoperative complications and re-transplantations

In the first 6 months, post-surgery, 29 (19.3%) eyes had graft detachment, 19 (12.7%) of them underwent re-bubbling. Only one of 11 eyes with minor graft detachment was re-bubbled and graft re-attachment was achieved. All 18 eyes with major graft detachment were re-bubbled nevertheless, graft re-attachment was achieved in 11 (7.3%) of them. Two eyes underwent PK, 5 eyes underwent re-DMEK. There was no

statistically significant difference between the rate of minor and major graft detachment development in patients who underwent phacoemulsification and those who did not. ($p=0.378$ and $p=0.216$, respectively).

PGF occurred in 11.3% (17/150) of the eyes, 8 of them had PK, and for 9 eyes, DMEK was repeated. The SGF rate was 9.3%, and all SGF occurred after 1-year follow-up of DMEK, with 8 eyes (57.1%) occurring between 1 and 3 years and 6 (42.9%) eyes occurring between 3 and 7 years. There were 4 eyes that developed SGF and also received a second graft, 5 eyes underwent PK, and 5 eyes rejected a second surgical operation. The postoperative allograft rejection rate was 4.7% (7/150), and 3 of those were treated with corticosteroid, while 4 eyes that was not responder to corticosteroid treatment was undergone PK (Table 5).

Discussion

In the last decade, DMEK has become a popular technique for the treatment of corneal endothelial dystrophies [16,17]. A number of cases are needed to gain experience on graft preparation and unrolling time for corneal surgeons to achieve a good standard of care. Nevertheless, DMEK has better graft survival rates than DSEK and PK [18].

According to Birbal *et al.* [4], the 5-year graft survival success of DMEK is 90%. Moreover, the cumulative mid-term graft survival rate was reported to be as high as 96%, which corroborates the 5-year graft survival rate reported by Schlögl *et al.* [3] and Baydoun *et al.* [19]. The results of Vasiliauskaitė *et al.* [12] suggested a 79% of graft survival rate of post-transplantation in 10 years. In this long-term study, we evaluated graft survival rates of 150 eyes and analysed risk factors that affected the outcomes. Overall, the graft survival rates of DMEK were as follows: 96% at the 6th month, 94% at the 3rd year, 88% at the 5th year, and 58% at the 7th year. Compared to the studies mentioned, our findings suggested a lower survival rate of corneal endothelial grafts. The reason for this might be that we included learning-curve cases in our study, and 59.3% of the study population was diagnosed with BK.

Many publications that generated short- and long-term outcomes for DMEK reported a significant improvement in visual acuity for the majority of cases. For example, Birbal *et al.* [4] achieved excellent visual outcomes within 6 months of transplantation. In a year, 73% of cases' BCVA scores improved by ≥ 2 Snellen lines, and by five years, the improvement was maintained [4,14]. According to Vasiliauskaitė *et al.* [12], even though there were differences in BCVA results in 1st, 5th, and 10th years post-transplantation, there was a significant increase in BCVA compared with the preoperational results. In our study, 62.6% of eyes had an increased BCVA by ≥ 2 Snellen lines in a year, but the long-term postoperative visual acuity results were lower than in the other studies. The reasons for this might be patients' delayed visits to the hospital before the surgery (despite their need for treatment) and patients' bad preoperative visual acuity. The delayed preoperative visit could affect the potential of the stroma to clear up without haze or scar after DMEK and so postoperative visual acuity may not increase.

Recent studies have shown a continued BCVA improvement in visual acuity from 6 months to 3 years postoperatively, but on the other hand, there might be selection bias due to geriatric patients, who have

lower BCVA in general and withdraw from continuous follow-up periods. In contrast, younger patients have more adherence to follow-up visits [11,18]. We also observed a positive correlation with BCVA (logMAR) and patients' age. In 6th the month visit, there was quite an increase in visual acuity, which was maintained for up to 3 years. Similar to the other studies, younger patients attended post-DMEK surveillance more than elderly recipients.

Postoperative ECD was negatively associated with DMEK, DSEK, and PK [4,12], and the highest ECD reduction was observed in 6th-month check-ups[18]. After DMEK, eyes operated on for FECD had less endothelial cell loss than those with BK and other corneal dysfunctions because of the donor endothelial cells' regenerative capacity [1,19,20]. During DMEK, difficulties in unrolling endothelial lamella and greater tissue manipulation could cause damage to cells and detachment of the graft [10]. In the case of graft detachment, air injection one time had no effect on ECD, two injections and more re-bubbling procedures might reduce ECD [15,21-26].

A negative correlation between graft storage time and ECD was reported by Birbal *et al.* [4], and ECD declined 37% in the first 6 months. However, this result had no statistical significance. In this study, ECD numbers had a negative correlation with the age of the patient and minor and major detachment, whereas re-bubbling had no significant effect on postoperative ECD.

The most important complication of DMEK in the first 6 months is graft detachment, which might have rates of up to 82% [9,23]. Minor graft detachment was seen twice as much as major detachment and five times more than full detachment [17]. Surgeons' experience with DMEK could reduce the occurrence of graft detachment, and decentred grafts and overlapped host-donor DMs may correlate with higher re-bubbling rates [17,23-25]. Upside-down grafts are one of the causes of detachment, and preoperative stamping is helpful to show the correct position of the graft (right side up) to avoid this complication of DMEK [15,26].

In this study, we used a single peripheral triangular marking as the graft marking technique, which is useful in cases with poor anterior chamber visibility. When endothelial cells are damaged during re-bubbling or peripheral partial detachment occurs, waiting for a while for spontaneous reattachment might overcome the problem. However, if the partial detachment is major and at the centre, or full detachment happens, then re-bubbling is required [21]. Re-bubbling increases the graft survival rate [6] and decreases re-transplantation rates [19,21,27], although there is no consensus on its timing. A delayed procedure might cause scarring on the DM [21].

Eyes that underwent re-bubbling once and primarily attached eyes had similar postoperative visual outcomes [27]. Minor and major detachment cases were re-bubbled from 1 day to 13 weeks [12]. Like in previous studies, in the present study, eyes that underwent re-bubbling once and primarily attached eyes had no significant differences in ECD and visual acuity outcomes. Eyes with minor detachment were followed for a mean of 6.92 ± 3.63 (3-14) days, and if the edema did not subside, they were re-bubbled. Re-bubbled eyes with major detachment were injected with an air bubble underneath the graft in the first

24-36 hours, and as a result, 61.1% of them benefited from the process, whereas 38.9% needed another DMEK or a PK.

Primary graft failure is an early post-DMEK complication. It is defined as corneal edema for a duration of 3-4 weeks [11,23,28]. SGF and allograft rejection constitute more severe complications that occur later after transplantation [11,23]. Despite graft rejections being associated with increased ECD loss, ECD loss is not a risk factor for graft failure [5]. Usually, SGF occurs after allograft rejection or persistent graft detachment [18]. Eyes that developed SGF had surgery-related endothelial cell loss. Although eyes retained sufficient ECD, they had failure, and the reasons might be DM storage conditions, manipulation-related functioning problems of the corneal graft, or endothelial cell shock [15].

SGF was observed in 6% of the study group and became the major complication in the long-term follow-up of corneal post-transplantation along with decreased ECD. Re-transplantation was performed for the management of SGF and graft detachment, and half of the cases were re-transplanted in a year [12,18]. We observed the progression of SGF in 9.3% of eyes and followed-up 57.14% of those for the first year. We performed a second transplantation on 64.3% of them.

DMEK has a lower risk for allograft rejection than PK or Descemet's stripping automated endothelial keratoplasty (DSAEK)/DSEK [29], and the estimated rejection probabilities are 0.9%, 2.3%, and 2.3% in 1, 2, and 4 years, respectively. The cumulative 5-year rejection episode rates were 2.6% and 4% [5,12]. Treatment of post-DMEK allograft rejection episodes with corticosteroids is better managed than other types of keratoplasty, and 4.7% of patients in the present study were diagnosed with an allograft rejection episode in 84-months of follow-up [4,5,12,18].

Despite the results of the study, its limitations are its retrospective design and the volunteer visits by the patients during the study period, which led to a lack of long-term data. In conclusion, DMEK is a corneal transplant option for patients with endothelial dysfunctions for long-term follow-ups. The reasons are its lower complication risk, better graft survival rate, and its therapeutic safety and efficacy. However, postoperative visual acuity might be affected by the patients' preoperative level of vision.

Declarations

Funding: No financial support was received.

Conflicts of interest: The authors declare that they have no conflict of interest.

Ethics approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was received from the Local Ethics Committee of Okmeydani Training and Research Hospital, Istanbul, Turkey.

Consent to participate: Written informed consent was obtained from all individual participants included in the study.

Consent for publication: Patients signed informed consent regarding publishing their data.

Availability of data and material: The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Code availability: Not applicable.

Authors' contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Nilay Kandemir Besek, Gulay Yalcinkaya, and Semih Cakmak. The first draft of the manuscript was written by Nilay Kandemir Besek and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

References

1. Melles GR, San Ong T, Ververs B, van der Wees J (2006) Descemet membrane endothelial keratoplasty (DMEK). *Cornea* 25: 987-990
2. Hamzaoglu EC, Straiko MD, Mayko ZM, Sáles CS, Terry MA (2015) The first 100 eyes of standardized Descemet stripping automated endothelial keratoplasty versus standardized Descemet membrane endothelial keratoplasty. *Ophthalmology* 122: 2193-2199
3. Schlögl A, Tourtas T, Kruse FE, Weller JM (2016) Long-term clinical outcome after Descemet membrane endothelial keratoplasty. *American Journal of Ophthalmology* 169: 218-226
4. Birbal RS, Dhubhghaill SN, Bourgonje VJ, Hanks J, Ham L, Jager MJ, Böhringer S, Oellerich S, Melles GR (2020) Five-year graft survival and clinical outcomes of 500 consecutive cases after Descemet membrane endothelial keratoplasty. *Cornea* 39: 290-297
5. Price MO, Fairchild KM, Price DA, Price Jr FW (2011) Descemet's stripping endothelial keratoplasty: five-year graft survival and endothelial cell loss. *Ophthalmology* 118: 725-729
6. Terry MA (2012) Endothelial keratoplasty: why aren't we all doing Descemet membrane endothelial keratoplasty? *LWW*.
7. Kruse FE, Laaser K, Cursiefen C, Heindl LM, Schlötzer-Schrehardt U, Riss S, Bachmann BO (2011) A stepwise approach to donor preparation and insertion increases safety and outcome of Descemet membrane endothelial keratoplasty. *Cornea* 30: 580-587
8. Cursiefen C (2013) Descemet membrane endothelial keratoplasty: the taming of the shrew. *JAMA ophthalmology* 131: 88-89

9. Dirisamer M, van Dijk K, Dapena I, Ham L, Oganer O, Frank LE, Melles GR (2012) Prevention and management of graft detachment in Descemet membrane endothelial keratoplasty. *Archives of ophthalmology* 130: 280-291
10. Maier A-KB, Gundlach E, Schroeter J, Klamann MK, Gonnermann J, Riechardt AI, Bertelmann E, Joussen AM, Torun N (2015) Influence of the difficulty of graft unfolding and attachment on the outcome in Descemet membrane endothelial keratoplasty. *Graefes Archive for Clinical and Experimental Ophthalmology* 253: 895-900
11. Droutsas K, Giallourous E, Melles GR, Chatzistefanou K, Sekundo W (2013) Descemet membrane endothelial keratoplasty: learning curve of a single surgeon. *Cornea* 32: 1075-1079
12. Vasiliauskaitė I, Oellerich S, Ham L, Dapena I, Baydoun L, van Dijk K, Melles GR (2020) Descemet Membrane Endothelial Keratoplasty: Ten-Year Graft Survival and Clinical Outcomes. *American Journal of Ophthalmology*
13. Lass JH, Szczotka-Flynn LB, Ayala AR, Benetz BA, Gal RL, Aldave AJ, Corrigan MM, Dunn SP, McCall TL, Pramanik S (2015) Cornea preservation time study: methods and potential impact on the cornea donor pool in the United States. *Cornea* 34: 601
14. Birbal RS, Parker J, Dirisamer M, Janicijevic A, Baydoun L, Dapena I, Melles GR (2018) Descemet membrane endothelial transfer: ultimate outcome. *Cornea* 37: 141-144
15. Bhogal M, Maurino V, Allan BD (2015) Use of a single peripheral triangular mark to ensure correct graft orientation in Descemet membrane endothelial keratoplasty. *Journal of Cataract & Refractive Surgery* 41: 2022-2024
16. Deng SX, Lee WB, Hammersmith KM, Kuo AN, Li JY, Shen JF, Weikert MP, Shtein RM (2018) Descemet membrane endothelial keratoplasty: safety and outcomes: a report by the American Academy of Ophthalmology. *Ophthalmology* 125: 295-310
17. Oellerich S, Baydoun L, Peraza-Nieves J, Ilyas A, Frank L, Binder PS, Melles GR (2017) Multicenter study of 6-month clinical outcomes after Descemet membrane endothelial keratoplasty. *Cornea* 36: 1467-1476
18. Ham L, Dapena I, Liarakos VS, Baydoun L, Van Dijk K, Ilyas A, Oellerich S, Melles GR (2016) Midterm results of Descemet membrane endothelial keratoplasty: 4 to 7 years clinical outcome. *American journal of ophthalmology* 171: 113-121
19. Baydoun L, Ham L, Borderie V, Dapena I, Hou J, Frank LE, Oellerich S, Melles GR (2015) Endothelial survival after Descemet membrane endothelial keratoplasty: effect of surgical indication and graft adherence status. *JAMA ophthalmology* 133: 1277-1285

20. Heinzelmann S, Böhlinger D, Eberwein P, Reinhard T, Maier P (2016) Outcomes of Descemet membrane endothelial keratoplasty, Descemet stripping automated endothelial keratoplasty and penetrating keratoplasty from a single centre study. *Graefe's Archive for Clinical and Experimental Ophthalmology* 254: 515-522
21. Gerber-Hollbach N, Baydoun L, López EF, Frank LE, Dapena I, Liarakos VS, Schaal S-C, Ham L, Oellerich S, Melles GR (2017) Clinical outcome of rebubbling for graft detachment after Descemet membrane endothelial keratoplasty. *Cornea* 36: 771-776
22. Feng MT, Price MO, Miller JM, Price Jr FW (2014) Air reinjection and endothelial cell density in Descemet membrane endothelial keratoplasty: five-year follow-up. *Journal of Cataract & Refractive Surgery* 40: 1116-1121
23. Rodríguez-Calvo-de-Mora M, Quilendrino R, Ham L, Liarakos VS, van Dijk K, Baydoun L, Dapena I, Oellerich S, Melles GR (2015) Clinical outcome of 500 consecutive cases undergoing Descemet's membrane endothelial keratoplasty. *Ophthalmology* 122: 464-470
24. Röck T, Bramkamp M, Bartz-Schmidt K, Röck D, Yörük E (2015) Causes that influence the detachment rate after Descemet membrane endothelial keratoplasty. *Graefe's Archive for Clinical and Experimental Ophthalmology* 253: 2217-2222
25. Tourtas T, Schlomberg J, Wessel JM, Bachmann BO, Schlötzer-Schrehardt U, Kruse FE (2014) Graft adhesion in descemet membrane endothelial keratoplasty dependent on size of removal of host's descemet membrane. *JAMA ophthalmology* 132: 155-161
26. Bachmann BO, Laaser K, Cursiefen C, Kruse FE (2010) A method to confirm correct orientation of descemet membrane during descemet membrane endothelial keratoplasty. *American journal of ophthalmology* 149: 922-925. e922
27. López EF, Baydoun L, Gerber-Hollbach N, Dapena I, Liarakos VS, Ham L, Melles GR (2016) Rebubbling techniques for graft detachment after Descemet membrane endothelial keratoplasty. *Cornea* 35: 759-764
28. Ham L, Van Der Wees J, Melles GR (2008) Causes of primary donor failure in Descemet membrane endothelial keratoplasty. *American journal of ophthalmology* 145: 639-644. e631
29. Anwar DS, Chu CY, Prasher P, Bowman RW, Mootha VV (2012) Features of Urrets-Zavalía syndrome after Descemet stripping automated endothelial keratoplasty. *Cornea*; 31:1330-1334

Tables

Table 1: Demographic and medical data of the study

Baseline Parameters	Mean $\pm$ SD / n-% (range)
Number of - eyes / patients	150 / 137
Eyes OD / OS	83 (55.3%) / 67 (44.7%)
Mean Follow-up (months)	36.71 $\pm$ 22.69 (6-87)
Gender	
Male	66 (43.7%)
Female	84 (55.6%)
Age (years)	65.90 $\pm$ 12.86
Diagnosis	
FECD	61 (40.7%)
BK	89 (59.3%)
Tamponade	
Air	79 (52.7%)
SF6	71 (47.3%)
Preoperative Lens Status	
Phakic	41 (27.3%)
Pseudophakic	109 (72.7%)
Donor cause of death	
Cardiovascular	71 (53.8%)
Respiratory	21 (15.9%)
Trauma	27 (20.5%)
Stroke	7 (5.3%)
Suicide	6 (4.5%)
Mean Graft storage time (days)	10.58 $\pm$ 1.92 (5-14)
Donor age (years)	53.34 $\pm$ 12.75 (19-74)

SD= Standard deviation; DMEK= Descemet membrane endothelial keratoplasty; FECD= Fuchs endothelial corneal dystrophy; BK= Bullous keratopathy

Table 2: Cumulative Survival Probability of Post-DMEK

Total	Time (months)	0	6th month	1st year	3rd year	5th year	7th year
	Cumulative survival probability						
	Estimate	-	0.96	0.95	0.94	0.88	0.58
	SE		0.018	0.019	0.02	0.03	0.06
	Cumulative events	0	5	6	7	13	33
Surgery Indication (BK vs FECD)							
	Time (months)	0	6th month	1st year	3rd year	5th year	7th year
BK	Cumulative survival probability						
	Estimate	-	0.94	0.92	0.81	0.58	0.42
	SE		0.02	0.03	0.05	0.07	0.09
	Cumulative events	0	4	5	11	20	24
FECD	Cumulative survival probability						
	Estimate	-	0.98	0.94	0.87	0.79	0.53
	SE		0.01	0.03	0.05	0.06	0.13
	Cumulative events	0	1	3	6	8	12

SE= Standard error; BK= Bullous keratopathy; FECD= Fuchs endothelial corneal dystrophy; *Cumulative survival probability during follow-up period

Table 3: Post-DMEK BCVA, ECD, and Pachymetry Results

Paramater	Pre-DMEK	6m FU	1y FU	3y FU	5y FU	7y FU
Mean BCVA ($\pm$ SD) (LogMAR) (min-max)	1.62 ($\pm$ 0.48) (0.40-3.00) (n:150)	0.73 ($\pm$ 0.51) (0.00-3.00) (n:148)	0.51 ($\pm$ 0.45) (0.00-3.00) (n:146)	0.38 ($\pm$ 0.26) (0.00-3.00) (n:82)	0.43 ($\pm$ 0.20) (0.05-1.30) (n:38)	0.38 ($\pm$ 0.25) (0.10-1.00) (n:20)
Mean BCVA ($\pm$ SD) in Snellen (decimal)	0.04 $\pm$ 0.07 (20/500) (n:150)	0.28 $\pm$ 0.20 (20/80) (n:148)	0.40 $\pm$ 0.21 (20/50) (n:146)	0.47 $\pm$ 0.21 (20/40) (n:82)	0.40 $\pm$ 0.16 (20/50) (n:38)	0.48 $\pm$ 0.19 (20/40) (n:20)
Mean ECD ($\pm$ SD) (cells/ mm ²)	2572 ($\pm$ 250) * (n:150)	1793 ($\pm$ 636) (n:106)	1688 ($\pm$ 626) (n:102)	1532 ($\pm$ 608) (n:67)	1310 ($\pm$ 525) (n:36)	1190 ($\pm$ 441) (n:19)
Mean ECD decrease ($\pm$ SD) (%)**		37.70 ($\pm$ 20.7)	42.58 ($\pm$ 19.04)	44.75($\pm$ 17.83)	47.49($\pm$ 13.60)	55.03($\pm$ 13.41)
Mean pachymety ($\pm$ SD)	665($\pm$ 126) (n:145)	568($\pm$ 102) (n:105)	572($\pm$ 93) (n:100)	572($\pm$ 91) (n:65)	575($\pm$ 94) (n:36)	578($\pm$ 54) (n:17)
Mean pachymety decrease ($\pm$ SD) %**		8.5 ($\pm$ 11.36)	7.35 ($\pm$ 10.88)	10.40($\pm$ 12.65)	9.32 ($\pm$ 13.40)	4.73 ($\pm$ 10.40)

m= months; y= years; FU= Follow-up; BCVA= Best corrected visual acuity; ECD= Endothelial cell density; SD= Standard deviation, n= Number of eyes; *Donor ECD, **Decrease: compared to preoperative values.

Table 4: Effects of the Covariates from Linear Mixed Models on Clinical Outcome after DMEK

BCVA(logMAR)	ECD	Pachymetry
--------------	-----	------------

	Coeff.	SE	<i>p</i>	Coeff.	SE	<i>p</i>	Coeff.	SE	<i>p</i>
Intercept	0.751	0.209	0.01	1719.28	229.46	0.01	543.77	63.04	0.01
Patient age (years)	0.00	0.00	0.009	-5.39	2.52	0.034	1.30	0.75	0.085
Gender Female vs Male	0.00	0.05	0.907	125.71	59.47	0.035	-0.78	20.61	0.970
Lens status phakic vs pseudophakic	-0.07	0.07	0.305	-4.92	82.75	0.953	-17.95	26.63	0.501
Indication BK vs FECD	0.18	0.06	0.006	-42.56	70.05	0.544	11.85	25.24	0.639
Minor (≤1/3 of graft surface area)	0.02	0.11	0.806	-268.61	123.89	0.031	-24.42	33.79	0.471
Major (>1/3 of graft surface area)	0.11	0.08	0.163	-409.65	86.11	0.01	-58.03	29.90	0.054

BCVA= Best corrected visual acuity; ECD= Endothelial cell density All eyes included in the statistical analyses (n:150); Bold numbers are statistically significant (*p* values ≤0.01); Coeff.= Coefficient regression (fixed effects); SE= Standard error

Table 5: Complications and re-interventions after DMEK

Interval of Occurrence		Time			
Occurrence	Short-term	Long- term			
Complication	n (%)	≤6m	6m - 1y	1y - 3y	3y - 7y
Detachment≤1/3	11 (7.3)	11			
Detachment>1/3	18 (12)	18			
PGF	17 (11.3)	17			
SGF	14 (9.3)	-		8	6
Allograft rejection	7 (4.7)	1	2	3	1
Re-interventions					
Re-bubbling	19 (12.7)	19			
Repeat DMEK	18 (12)	5	6	7	
PK	19 (12.7)	3	7	6	3

n= Number of eyes; m= months; y= years; PGF= Primary graft failure; SGF= Secondary graft failure; DMEK= Descemet membrane endothelial keratoplasty; PK= penetrating keratoplasty

Figures

Figure 1

Kaplan–Meier curves showing the cumulative survival probabilities for DMEK eyes.

Figure 2

Kaplan Meier analysis of the subgroups showing the cumulative survival probabilities.