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Review

Evolving Techniques and Indications of Descemet Membrane Endothelial Keratoplasty

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Abstract

Endothelial keratoplasty has replaced traditional penetrating keratoplasty for the treatment of corneal endothelial dysfunction. It offers faster, more predictable, stable visual recovery and low rejection rates while the surgery itself is less invasive. Descemet membrane endothelial keratoplasty (DMEK) is currently the gold standard for the treatment of Fuchs endothelial dystrophy, bullous keratopathy, and corneal edema after cataract surgery. Its favorable long-term outcomes are increasingly reported by large study groups. This review summarizes the current literature on new DMEK techniques, including size and shape modifications, new graft delivery techniques, and surgical pearls for challenging cases like eyes with glaucoma, glaucoma tubes, and failed penetrating keratoplasties.
Keywords: Corneal transplantation, DMEK, hemi-DMEK, quarter-DMEK, DMEK in complicated cases

Introduction

Endothelial keratoplasty (EK) offers great advantages for the treatment of patients with endothelial dysfunction. It can be performed for Fuchs endothelial dystrophy, pseudophakic or aphakic bullous keratopathy, posterior polymorphous dystrophy, iridocorneal endothelial syndrome, or failed penetrating keratoplasty (PK). It provides more rapid visual recovery, lower rejection rates, better refractive outcomes, and greater structural integrity than traditional PK.[1,2,3,4] Moreover, it provides a closed system that prevents PK's most dreadful complication: intraoperative suprachoroidal hemorrhage.[5,6]

Modern EK techniques include mainly Descemet stripping automated EK (DSAEK), Descemet membrane EK (DMEK), and pre-Descemet EK (PDEK).[7] In 2006, Melles[1] first introduced DMEK that selectively replaces the Descemet membrane (DM) and endothelium, resulting in an anatomically accurate procedure. DMEK poses some technical challenges, such as the need for careful graft preparation and meticulous graft orientation techniques, which result in a steep learning curve.[8] Despite this, DMEK has gained popularity in the last decade, and various modifications have been introduced that are gradually improving the surgical technique or donor preparation in challenging situations.[9]

As DMEK surgery became more popular, more information on its mid- and long-term results also became available. Recently, Birbal et al.[10] reported outcomes for a cohort of 500 DMEK eyes with a 5-year graft survival probability of 0.90 and 82% of eyes achieving a best-corrected visual acuity (BCVA) of 20/25. The endothelial loss was 37% in the first 6 months, 40% at 1 year, and 55% at 5 years. Allograft rejection rates were as low as 1.7-2.8% compared to 5% in DSAEK and 14% in PK.[10] Woo et al.[5] compared DMEK survival at 5 years (97.4%) with DSAEK (76.4%) and PK (54.6%). Even after 10 years, pioneering DMEK surgery cases maintained excellent visual acuities with low rejection rates, further supporting DMEK as the gold standard treatment for corneal endothelial diseases.[11]

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In this review, we will discuss new perspectives, various indications of DMEK, and elucidate the surgical steps of DMEK in challenging cases in light of recent scientific publications.

New Techniques of Graft Preparation and Insertion

Hemi-DMEK

DMEK provides fast visual recovery in the treatment of endothelial dysfunction. However, a donor corneal tissue with good endothelial cell density is required for the procedure.[12,13] Due to the worldwide shortage of suitable donor tissue for EK procedures, the idea of splitting the donor tissue into two or more grafts while keeping similar surgical success evolved (Table 1).[14] Lam et al.[15] were the first to describe a half-moon (semicircular) hemi-DMEK technique. In regular DMEK surgery, an 8.0 mm graft is sufficient to achieve corneal clarity. A hemi-DMEK graft utilizes a larger diameter graft, like 11-12 mm, and divides it into two. This way, the surface area of a hemi-DMEK graft and the number of transplanted corneal endothelial cells are comparable to regular DMEK. Although it is advantageous in terms of tissue efficiency, it presents some challenges in preparation and intraocular graft positioning. In this technique, after mounting the corneoscleral buttons endothelial side up, uveal remnants are removed and the DM is loosened with a knife in the central direction. Then the buttons are separated into two halves and the DM is removed from the posterior stroma as two half-moon shaped grafts without any trephination.[16] Except for the diameter of the graft, a routine DMEK surgery is performed. While orienting the graft, the widest diameter is aligned to the longest horizontal meridian so that the largest part of the graft covered the pupillary area (Figure 1a).

The healing period also has unique properties. Some denuded corneal stroma is left after surgery because of the mismatch between the descemetorhexis area and the graft. Clinically, the postoperative corneal edema resolves in 12 months and the denuded area is covered with endothelial cells. It is still not clear whether the posterior denuded stroma is covered via the migration of donor or recipient endothelial cells.[17] Müller et al.[18] showed that endothelial cell density was decreased by 59% in the first year and stayed stable for 3 years. Visual acuity was improved, and no complications were seen intraoperatively or postoperatively. The corneas were clear and presented with stable pachymetry in 1- and 3-year clinical follow-ups.[18,19] Hemi-DMEK led to similar outcomes to conventional DMEK; therefore, it may be a promising technique due to its potential to double the number of endothelial transplants from the same donor cornea.

Quarter-DMEK

The idea of stromal repopulation by host endothelial cells after a complete Descemet graft detachment or "descemetorhexis only" (descemetorhexis without EK) surgery helped to design a technique called "quarter-DMEK."[20,21] Since host cellular migration is slow in patients with descemetorhexis only, quarter-DMEK could be described as a hybrid technique that combines the advantage of DMEK (achieving rapid corneal clearance) with DM endothelial transfer (DMET) (stimulates peripheral host endothelium). One donor cornea can yield four endothelial grafts by this procedure. Zygoura et al.[20] evaluated the outcome of quarter-DMEK applied in 12 patients with central Fuchs endothelial dystrophy. As in hemi-DMEK, the corneoscleral buttons were mounted endothelial side up, uveal remnants were removed, and the DM was loosened with a knife in a central direction. However, the buttons were then separated into four equal parts and the DM was removed from the posterior stroma as four equal grafts. All DM grafts were rolled with the endothelium on the outside and kept in an organ culture medium until transplantation. After a 7-8 mm descemetorhexis under air, routine DMEK surgery was performed with the graft oriented centrally (Figure 1b). They followed the patients for 6 months and reported that all of the eyes reached a BCVA of ≥20/40 (≥0.5) and 11 of 12 eyes (92%) achieved a BCVA of ≥20/25 (≥0.8). The rebubbling rate was 33% within the first 2 months. However, they showed a quick drop in endothelial cell density in the first month. Extensive endothelial cell migration and error of measurement at the graft edges could be the reason for this drop. The authors also described a higher tendency for corneal clearance along the cut edges of the grafts compared to the "limbal" rounded edge, which may reflect different cell migration patterns in different graft areas. It was hypothesized

Table 1. Modifications of standard Descemet membrane endothelial keratoplasty (DMEK) surgery

Type of DMEK	Difference from standard DMEK	Advantage	Disadvantage	Defined by
Hemi-DMEK	Uses half of a larger sized graft	2 grafts from one donor	Challenges with graft preparation and positioning	Melles et al.[1]
Quarter-DMEK	Uses a quarter of a larger sized graft	4 grafts from one donor	Challenges with graft preparation and positioning	Melles et al.[1]
¾-DMEK	Uses three quarters of a larger sized graft	Can be used in the presence of tubes in the anterior chamber	Challenges with graft preparation and positioning	Melles et al.[1]
E-DMEK (EndoGlide)	The graft is prepared the same way but folded "endothelium-in"	Easier unfolding, especially in challenging cases	Requires special cartridge for delivery	Mehta et al.
H-DMEK (Hybrid)	Similar to E-DMEK, the graft is prepared with a thin stroma that acts like a carrier	Easier unfolding, especially in challenging cases	Requires 4.5 mm corneal incision, challenging graft preparation	Woo et al.[5]

DMEK: Descemet membrane endothelial keratoplasty

that the repopulating cells at the rounded graft edges were probably host endothelial cells.

Birbal et al.[22] reported the clinical outcomes of 19 patients with central Fuchs endothelial dystrophy. These patients showed good visual outcomes, and the visual acuities were stable for 2 years postoperatively. Eight of 19 eyes (42%) required rebubbling due to significant graft detachment. Good outcomes of quarter-DMEK were also reported by Oganesyan et al.[23] Quarter-DMEK may be comparable to conventional DMEK in terms of visual acuity outcomes and increase the availability of endothelial grafts.[22]

E-DMEK

Despite the many advantages of DMEK, technical difficulties in graft insertion and unfolding led to a new surgical technique called EndoGlide-DMEK (E-DMEK).[24,25] This technique features several differences in graft preparation and insertion. In this technique, the graft is prepared in a standard manner,

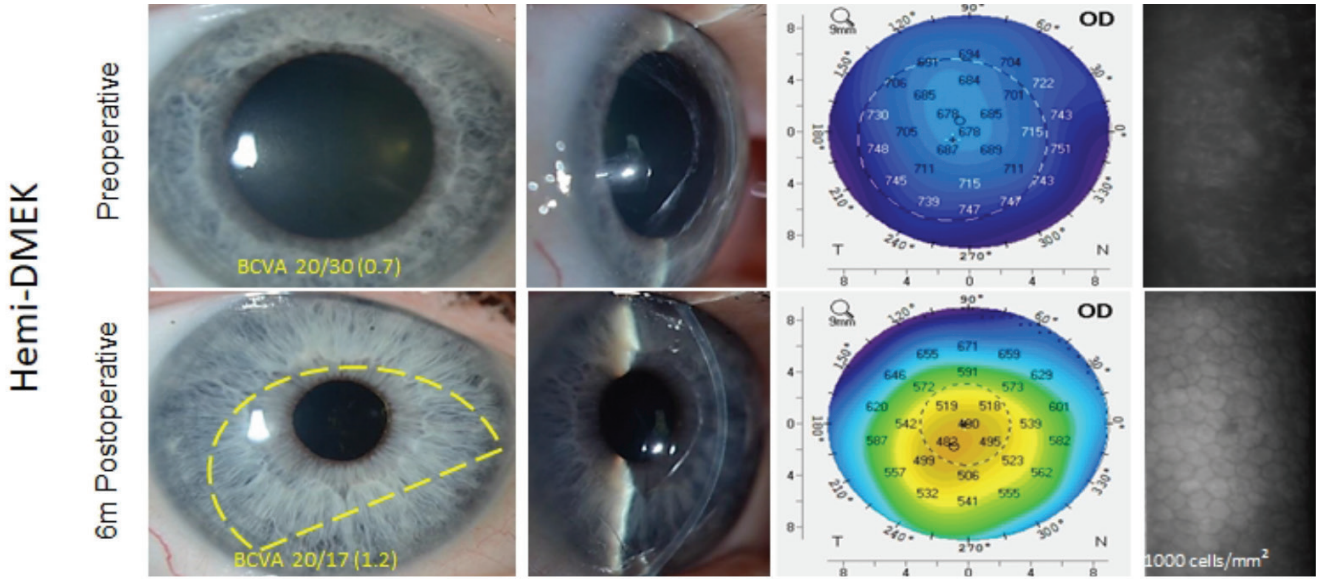

Figure 1a. Slit-lamp images, pachymetry maps, and specular microscopy images before and after hemi-DMEK (Descemet membrane endothelial keratoplasty). Images obtained preoperatively and at 6 months postoperatively are shown. The dashed yellow lines show the position of the hemi-DMEK grafts

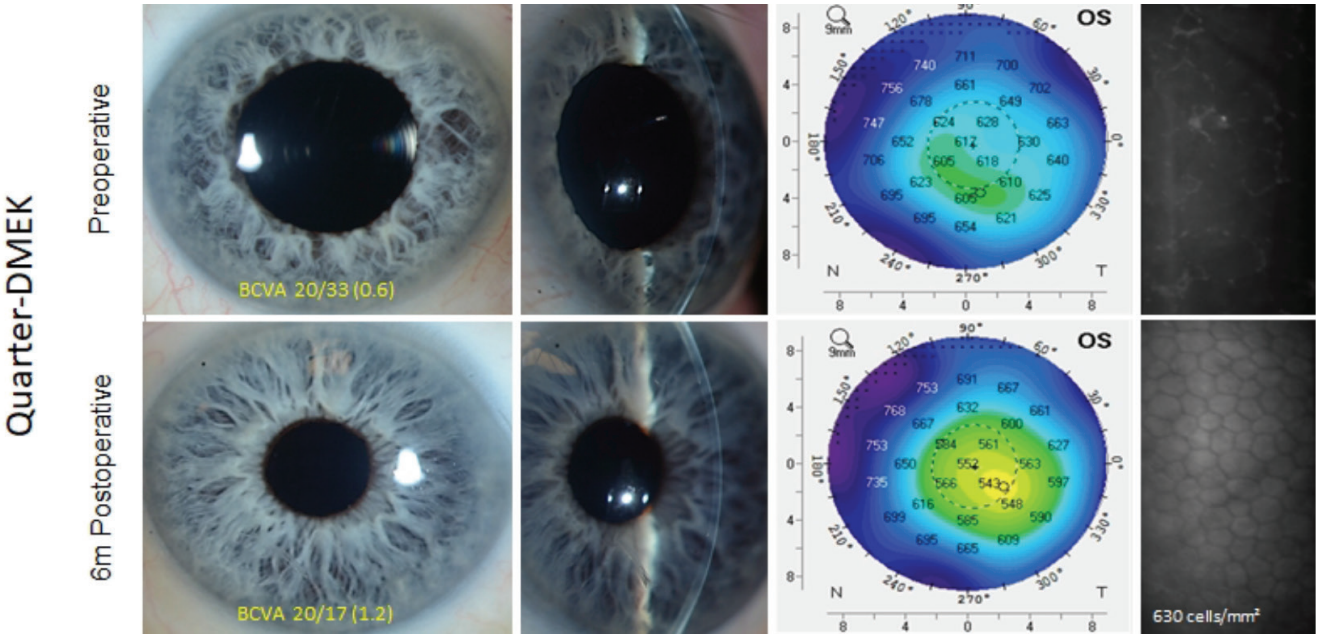

Figure 1b. Slit-lamp images, pachymetry maps, and specular microscopy images before and after quarter-DMEK (Descemet membrane endothelial keratoplasty). Images obtained preoperatively and at 6 months postoperatively are shown

but it is tri-folded in an endothelium-in fashion using a forceps rather than the natural endothelium-out orientation. It is then loaded in a cartridge and inserted through a corneal incision (Figure 2a-f). Rather than being injected, it is pulled into the anterior chamber (AC) by grasping with a forceps from the opposing corneal incision. Once an endothelium-in graft enters the AC, it unfolds easily with fewer maneuvers. Keeping the AC shallow is critical for this technique as the graft would scroll back to the endothelium-out orientation in a deep AC. E-DMEK is especially designed for challenging cases like those with abnormal anterior segment anatomy, gross peripheral anterior synechia, drainage devices, and filtering blebs. It is similar to DSAEK graft insertion, so it may be technically easier for surgeons who are accustomed to DSAEK surgery during the transition to DMEK surgery.

Tan et al.[24] showed both *ex vivo* and clinical results of E-DMEK. In an *ex vivo* study, DMEK grafts were stained with calcein acetoxymethyl, tri-folded in the endothelium-in fashion, and placed into the EndoGlide. Then they were pulled through and unfolded in imaging dishes simulating a real surgery. Mean endothelial cell loss was 15.2%±5.4% in 9 human corneas. In a clinical series, endothelial cell loss was 33.6% (range 7.5%-80.4%) among 69 eyes with at least 6 months follow-up. Rebubbling and primary graft failure rates were 11.6% and 1.5%, respectively. In conclusion, they suggested E-DMEK was a safe and promising alternative to standard DMEK due to its good clinical outcomes.

H-DMEK

Woo et al.[26] developed a new technique called hybrid DMEK (H-DMEK). They used the DSAEK pull-through donor inserter and donor stroma as a carrier while performing DMEK. In this technique, pre-cut DSAEK donor tissue from the eye bank that was approximately 150 µm in thickness was utilized. During graft preparation, a Tan DMEK stripper was used for lamellar dissection of the DM from the underlying stroma, but the DM was not completely removed from the stroma. The DMEK graft and stromal carrier were loaded into the EndoGlide inserter device in a double-coil endothelium-in configuration. The glide was inverted so that the graft would be placed in an endothelium-down fashion. It was inserted through a scleral tunnel into the AC. The DMEK graft edge was pulled with forceps from the nasal paracentesis incision into the AC, completely detaching from the donor stroma and leaving the stroma behind.

H-DMEK is similar to E-DMEK as the graft is placed in an endothelium-in fashion. The difference is the presence of a thin stromal component during graft preparation. The thin stroma acts like a carrier of the DMEK graft. This difference makes it easier to handle and fold the graft while placing it in the basin. The need for a 4.5 mm incision to deliver the graft into the AC and more complicated steps in graft preparation are potential disadvantages.

Eighty-five eyes of 79 patients with Fuchs endothelial dystrophy or bullous keratopathy were involved in the clinical study. Of the eyes without pre-existing ocular pathology, 44.7% and 57.1% showed a BCVA of 20/25 or better at 6 and 12 months postoperatively, respectively. Endothelial cell loss was 32.2% at 6 months. The authors suggested that this technique might be useful in complicated cases.[26]

DMEK in Vitrectomized Eyes

Although DMEK surgery is gaining popularity for endothelial dysfunction, vitrectomized eyes undergoing DMEK still pose a challenge. Due to the lack of posterior support of the vitreous, the AC is mostly deep, and graft unfolding can be difficult. Excessive manipulation of the donor tissue while

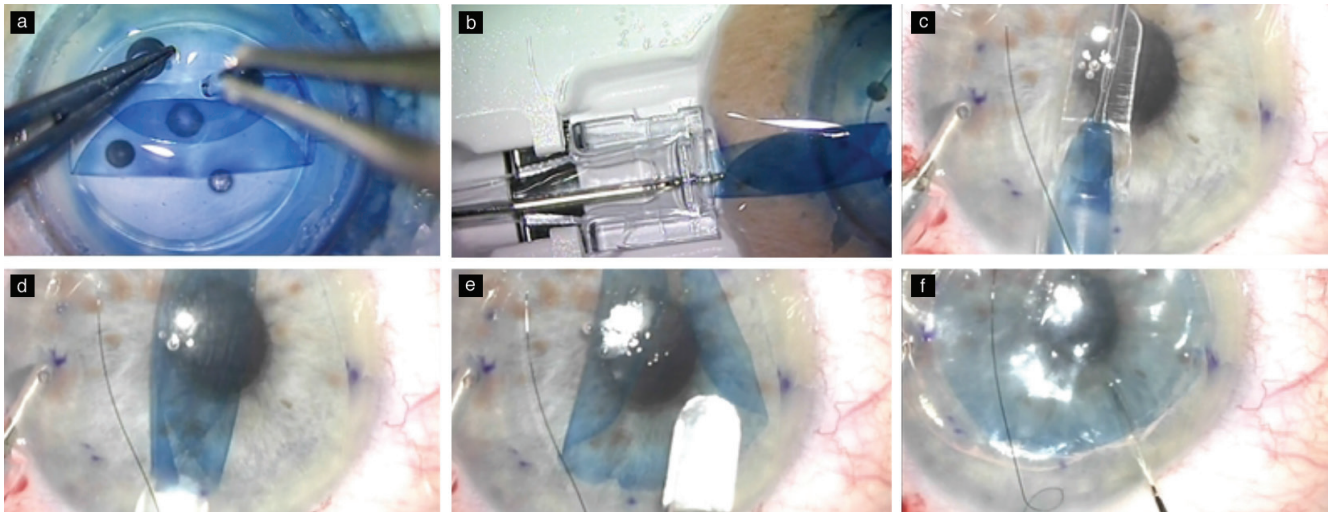

Figure 2. Steps of the Endoglide Descemet membrane endothelial keratoplasty (E-DMEK) procedure. a) Formation of tri-fold using the no endothelium touch technique. b) Loading the DMEK graft into the DMEK Endoglide using 23G straight forceps. c) Inserting the DMEK Endoglide into the anterior chamber (AC) through a 2.6 mm clear corneal incision. Pre-placed tissue will be used. The double-port 23G AC maintainer (ASICO) ensures the AC can be deepened as needed; d) As the graft is pulled in, it will spontaneously unfold endothelium side down in a deep AC because it naturally wants to scroll endothelium-out. e) As the graft opens, the cornea can be gently tapped to enhance the opening of the posterior leaves of the graft if needed. f) Once the graft has opened, the bubble is enlarged with more gas

unfolding may lead to graft failure.[27] Additionally, the injected air bubble used to tamponade the graft toward the stroma may be less effective due to a fluctuating iris-lens diaphragm.[28] As injected air tends to move posteriorly, recurrent globe collapse is a significant problem. Furthermore, the DMEK graft may dislocate into the vitreous cavity.[29,30] However, the challenges should not discourage surgeons from proceeding with DMEK, as some surgical modifications have been described for these eyes to improve the outcome. The main philosophy for DMEK graft unfolding relies on a shallow and stable AC. Moreover, donor age is important in these eyes. Age-dependent decrease in elastin levels, change in collagen composition, and increase in nonenzymatic glycosylation cause an increase in DM rigidity.[31] Therefore, older donor grafts unfold more easily and are more appropriate for these eyes.

Yoeruek et al.[32] tried a new maneuver for unfolding the graft in high myopic vitrectomized eyes. After inserting the DMEK graft, they performed equatorial digital indentation and corneal tapping for unfolding. During this maneuver, they avoided using air injection above or below the graft.[32] After centration and unfolding, air was injected below the graft for apposition against the posterior stroma. The AC was filled totally with air. They first published their results in a case series with 6 Fuchs endothelial dystrophy and 4 bullous keratopathy eyes.[32] Three of 10 eyes had graft detachment and required rebubbling, but they showed no graft failure during the follow-up period. Although this technique worked quite well for Fuchs endothelial dystrophy and bullous keratopathy eyes, they had difficulties in vitrectomized eyes. Their retrospective clinical study of 20 vitrectomized eyes that underwent DMEK surgery showed that 13 of them had significant intraoperative complications.[29] Intraoperative corrective measures were quite difficult in a few cases, and iatrogenic intraocular damage was encountered in some of them. Unfolding the graft was quite difficult. Eleven eyes had graft dislocation and two had iatrogenic primary graft failure.

Sorkin et al.[27] performed DMEK in vitrectomized eyes using posterior pars plana infusion. In this technique, after DMEK grafts were prepared with an "F" marking,[33] a 23-gauge trocar was inserted at the inferotemporal quadrant, 3.0 mm from the limbus. Infusion pressure was set between 5-26 mmHg depending on the stability of the AC. After descemetorhexis, a glass pipette or intraocular lens (IOL) injector was used to deliver the graft. The pars plana infusion was turned on and off to maintain optimal eye pressure and a shallow AC. This facilitated graft unfolding and positioning. Yoeruek's tapping technique (corneal tapping with external digital pressure application) was used during the unfolding.[32] After the graft was unrolled and positioned, the posterior infusion was turned off and the AC was filled with air. The trocar was extracted from the eye, and corneal incisions and any leaky sclerotomy sites were sutured. The authors performed this technique on 12 vitrectomized eyes and had one graft detachment, which required rebubbling.[27] No graft failure was experienced during the follow-up period. Another study by the same group evaluated the long-term outcomes up to 2 years.[28] They reported 5 of 15 eyes had retinal complications, including retinal detachment, retinoschisis, and cystoid macular edema. Although using posterior pars plana infusion could potentially reduce intraoperative and postoperative complications in vitrectomized eyes, the authors also cautioned that using an infusion could increase retinal complication risks.

Some of the vitrectomized eyes may also have sutured IOLs. In these patients, several maneuvers may be required to unfold the DMEK graft.[32,34] These eyes are monocameral, and this situation may lead the graft to migrate to the posterior cavity. Additionally, the globe is prone to collapse, which makes graft unfolding quite difficult.[27,29,35] Hayashi et al.[36] described a modified technique called the "double-bubble technique in DMEK for vitrectomized eyes." It was the modification of a small air bubble-assisted unrolling maneuver (Dapena maneuver).[37] In this technique, after inserting the DMEK graft, one small air bubble was placed over the graft for unfolding, and the other large bubble was injected beneath the graft for fixation. If peripheral edges were not attached, they applied bubble-bumping maneuvers to unfold the edges. Despite the unfolding time being relatively long, all of the surgeries were successful. In the follow-up period, one eye required rebubbling.

Although using 23-gauge infusion helps to stabilize the globe, unfolding the donor graft is still a problem due to its strong recurling tendency. The equatorial digital indentation and corneal tapping techniques are helpful mainly in partially vitrectomized eyes. Eyes with completely removed vitreous still pose several challenges. In the normal eye, the vitreous applies a counter-pressure and limits the motion of the iris-lens diaphragm. As iris-lens diaphragm stability is necessary for DMEK surgery, Yoeruek et al.[38] described a new technique using a temporary diaphragm for easier graft unfolding. Following descemetorhexis, a hydrophilic methacrylate sheet measuring 12.8 mm with holes in the periphery was implanted into the AC to create a double AC. A DMEK graft was injected into the AC over the hydrophilic methacrylate sheet and unfolded. Under continuous air injection through a 30-gauge cannula, the hydrophilic methacrylate sheet was removed. Sulfur hexafluoride gas at a concentration of 20% was preferred for longer tamponade. Seven eyes of 7 patients who underwent DMEK by this method showed no complications intraoperatively or postoperatively. Karadağ et al.[39] tried using the posterior corneal stroma instead of a hydrophilic methacrylate sheet for the same purpose.

Saad et al.[40] described the C-press technique in 11 eyes of 11 patients who underwent DMEK. They reported that their experience with pars plana infusion and double-bubble technique in vitrectomized eyes were not reproducible in all cases; therefore, another new approach was required. Following descemetorhexis and DMEK graft insertion into the AC, correct graft orientation was ascertained by intraoperative optic coherence tomography. A cannula was then inserted inside the graft (Descemet side) and moved right and left to open it by irrigating with balanced salt solution. At the same time, a second cannula held in the other hand pressed externally on the central cornea. Shallowing the

AC with this pressure helped the graft to remain open. Then the first cannula was removed and 20% SF6 gas was injected. No intraoperative complications were experienced; however, 2 cases needed rebubbling for partial graft detachment. Lower unfolding time and complication rates were advantages of this technique.

These evolving techniques show that we do not have a standard, straightforward approach suitable for all vitrectomized eyes. It is advisable to get familiar with different methods so they can be readily applied when needed.

DMEK After Failed PK

After PK, secondary graft failure and late endothelial decompensation are likely to increase with the aging graft. In the past, the only options were repeating PK and implanting keratoprosthesis for managing failed PK.[41,42] Recently, EK has allowed restoration of endothelial function in failed PK grafts and decreased the need for a full-thickness graft. This reduces the risk of rejection and refractive changes and avoids the complications associated with "open-sky" surgery.[43,44,45,46] DMEK has acceptable outcomes in patients with failed PK. However, recent literature shows that it is associated with a high postoperative graft detachment rate, ranging between 26-100%.[45,46,47,48] Nevertheless, since the DMEK graft is thin and flexible, a better apposition could be achieved with DMEK-grafts compared to the "stiffer" DSAEK graft. Also, DMEK grafts should better fit the irregular posterior surface and PK wound and could cover more surface area.[49] Lavy et al.[46] evaluated the clinical outcomes of 11 DMEK surgeries for secondary PK failure. They described some surgical modifications and specific manipulations while performing DMEK in these patients. A corneal incision 3.0 mm wide was made in the host peripheral corneal rim without penetrating PK graft to avoid potential host-graft wound dehiscence. Descemetorhexis was started in the central area of the PK graft and was enlarged in a curvilinear pattern, like capsulorhexis, under air using a reverse Sinskey hook. The remaining part of the surgery was routine DMEK surgery (Figure 3a). The authors mentioned that circular scarring at the PK graft-host junction sometimes blurred the edges of the DMEK graft, and visualization was not always possible. Four of 11 eyes required rebubbling, and 7 of 11 eyes were clear at their last visit. Additionally, they showed that graft attachment could be achieved in eyes with failed PK grafts through interface scarring that was detected in histopathological specimens after the patient's death. The specimens with areas of detachment clinically showed a layer of newly formed fibrotic tissue extending from the PK wound area to the central and peripheral graft areas. Although the scar tissue formation may be a normal wound-healing process, the fibrotic response was more aggressive than in primary DMEK eyes, resulting in diffuse interface haze. Overall, three important points were emphasized: there may be delayed DMEK graft detachment, which may need rebubbling. Second, oversized DMEK grafts were more prone to detach. Third, pressurizing the eye adequately at the end of the surgery is critical. Otherwise, hypotony could lead to detachment of the graft.

Pasari et al.[42] reviewed 93 DMEK procedures performed in 84 eyes of 77 patients with failed PK. Stripping was done within the edge of the PK wound and avoiding the graft-host junction. Failed PK graft diameter, recipient horizontal corneal white-to-white diameter, and AC depth were evaluated intraoperatively to select the donor graft diameter. The graft was oversized, same-sized, or undersized. The 4-year graft survival rate of these patients was found to be 76%. They also showed that previous glaucoma surgery was the only risk factor for graft failure. Additionally, rebubbling rates changed depending on graft size. The rates were 53% when the DMEK graft diameter was oversized, 27% when same-sized, and 33% when undersized.

DMEK surgery under a failed PK may be challenging due to DM tags or stromal fibers caused by traumatic DM stripping. The maneuvers may affect DM graft adhesion and increase graft detachment risk. Some authors claimed DMEK could be done without removing the DM of the failed graft.[50] Alio Del Barrio et al.[51] performed non-Descemet stripping DMEK (NS-DMEK) and recommended either matched or undersized 0.25-0.50 mm grafts to avoid the PK donor-host junction. They also used SF6 tamponade to decrease the risk of graft detachment. All eight patients in the study achieved full PK transparency within two weeks. One patient required rebubbling, and one required PK re-suturing due to host-donor junction dehiscence. With this technique, DMEK surgery in failed PK patients was simplified and intraoperative complications were avoided.

Recently, femtosecond laser-assisted descemetorhexis has been recommended in patients with failed PK who do not have stromal scarring and have normal AC anatomy.[27,52,53] Sorkin et al.[54] performed femtosecond laser-assisted DMEK for failed PK in 8 patients. In this technique, descemetorhexis was planned 0.25 mm smaller than the PK graft to prevent graft dehiscence and incomplete incision.[55] The Intralase iFS femtosecond laser platform enabled a precisely located deep vertical ring cut.[53] Then, the DM was removed from the stroma using a reverse Sinskey hook. Deep dissection into the stroma was avoided. The remainder of the surgery was similar to standard DMEK. In this study, no cases required re-bubbling, and only one eye (12.5%) had a small graft detachment, which did not affect corneal clarity and vision. The same group compared manual (M) and femtosecond laser-assisted (F) DMEK for failed PK.[56] They showed that F-DMEK was effective and safe in failed PK patients, and rebubbling rates were lower than for M-DMEK. Primary failure was lower in F-DMEK; however, there was no significant difference compared to M-DMEK. Visual outcomes and postoperative cell densities were similar between the groups. Although the precise reason for the reduced detachment rate is unclear, they suggested that F-DMEK could lead to complete removal of the host's DM with less remnant Descemet tags and islands. In addition, the host DM peripheral to the descemetorhexis remains undamaged. While

F-DMEK looks promising, the data is currently limited to 10 patients.

DMEK in Eyes with Prior Glaucoma Surgery

Glaucoma predisposes a high risk for graft failure in either PK, DSAEK, or DMEK due to both surgical and immunological challenges. Technically it is more challenging to position a DMEK graft in the setting of previous glaucoma surgery because these eyes usually have comorbidities like synechia, aphakia, tubes, or pupillary abnormalities that need several surgeries.[57] It is harder to keep the air in the AC. These technical difficulties also result in prolonged surgical time and extra maneuvers, resulting in increased endothelial loss which leads to secondary graft failure. Lysis of anterior synechia and trimming the tube are some of the additional techniques used in these complex eyes. Immunologically, eyes also lose their immune privilege after glaucoma surgery because it alters the aqueous composition.[58]

Arevena et al.[57] reported early outcomes of DMEK in eyes with previous trabeculectomy or a drainage device. Surprisingly, they did not encounter secondary failures in the first postoperative year. After Birbal et al.[59] described the decrease of graft survival from 89% at 1 year to 67% at 2 years, similar studies on this subject emerged. Pasari et al.[42] showed graft survival probability gradually decreased from 78% at 1 year to 39% at 3 years. Sorkin et al.[60] investigated graft survival at 4 years based on previous studies showing a possible downward trend of graft survival over time. They found a survival drop over the third and fourth postoperative years, with cumulative 2-, 3-, and 4-year DMEK survival probability rates of 60%, 43%, and 27%, respectively.[28,57,61] Although eyes without glaucoma drainage devices (GDD) have better graft survival than eyes with GDD, they are more prone to graft failure than the control group, suggesting that glaucoma itself affects the long-term survival of DMEK grafts. Beyond graft failure, they found a significantly high rejection rate compared to the control group (19.6% vs. 2.3%, p=0.01).[60] The baseline high inflammatory status of eyes with previous glaucoma surgery due to disruption of the blood-aqueous barrier may be one of the reasons leading to this difference.

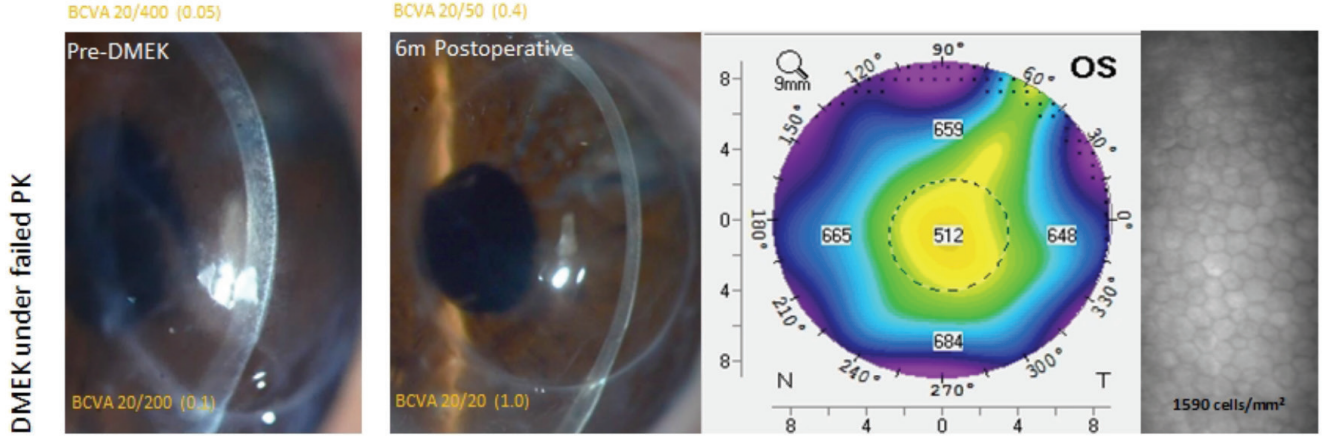

Figure 3a. Slit-lamp images before and after Descemet membrane endothelial keratoplasty, postoperative pachymetry map and specular microscopy image of an eye with a failed penetrating keratoplasty graft

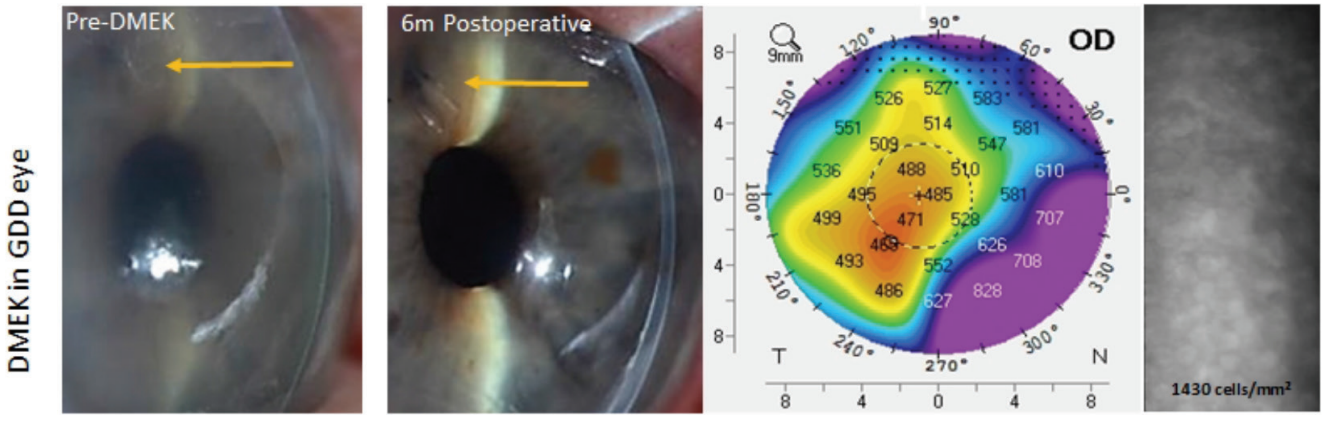

Figure 3b. Slit-lamp images before and after Descemet membrane endothelial keratoplasty, postoperative pachymetry map and specular microscopy image of an eye with a glaucoma drainage device superotemporally (orange arrows)

Endothelial cell loss is another important consideration in patients with prior glaucoma surgery. In addition to rejection-related cell loss, alterations of the aqueous environment may also contribute to ongoing cell loss in these eyes.[58] Aravena et al.[57] showed that endothelial cell loss was higher in the surgery group (44.6%±17.8%) than in the medically treated group (29.9%±12.0%) and the control group (32.7%±11.3%, p=0.001). Some potential factors such as inflammation, oxidative stress, and increased plasma proteins are included in endothelial apoptosis after glaucoma surgery.[62,63] Sorkin et al.[60] touched on another point about the trend of endothelial cell loss. Endothelial cell loss was highest in the first 6 postoperative months (about 44%), which was not different from other DMEK cases. After that, endothelial cell loss was higher in patients with glaucoma, about 12%-22%. The significant difference in endothelial cell loss continued throughout follow-up.

Apart from glaucoma surgery itself, the tube's position is quite important for graft survival and endothelial cell loss. Intermittent tube-uveal contact may result in corneal endothelial damage. Therefore, some technical modifications are recommended for GDD patients. The area of the GDD should be avoided while creating a 3.0 mm clear corneal incision at 12 o'clock position, and the superior conjunctiva was avoided for future glaucoma surgery. During graft insertion, contact between graft and tube should be prevented. The tube could be trimmed for better graft positioning. Additionally, Descemet graft unfolding should be performed over the tube, not over the iris (Figure 3b). This could be difficult in some cases; therefore, a modified "three-quarter DMEK technique" (3/4-DMEK) was designed and evaluated in three patients by Oganesyan et al.[64] All of the patients had previous Ahmed valve implantation and were pseudophakic. During graft preparation, the DM was stripped from the posterior stroma and put over a soft contact lens. Two perpendicular cuts with a keratome (MANI Inc, Tokyo, Japan) helped separate a quarter of the graft and create a 3/4-DMEK graft. In the host cornea, an 11-12 mm diameter descemetorhexis was performed, sparing the area under the GDD. While unfolding the graft, the missing 1/4-graft area was adjusted to the region of the tube, and the 3/4-DMEK graft was positioned centrally. The AC was filled 100% with air. All of the DMEK surgeries were uneventful, and grafts were stable up to postoperative 24 months. Endothelial cell loss was similar to previous studies (range 49%-64%) within the first year, as with conventional DMEK.[59,60,65] The absence of the graft under the tube prevented direct tube contact with the graft and may be beneficial for the graft's postoperative survival. Possible cell migration from the graft to the recipient stroma was minimized by leaving the host DM intact under the tube. Despite the promising results of this technique, they suggested the need for long-term follow-ups and larger case series.

The mechanical effect of the GDD, active filtration of air through filtering ostium or tube, and posterior escape of air through a large iridectomy are some of the factors blamed for high graft detachment and rebubbling rates (22.0%-23.5%).[57,59] Contrary to this popular belief, Sorkin et al.[60] did not find increased detachment and rebubble rates in these patients. They also stated that preoperative visual potential estimation of glaucomatous eyes was a challenge due to unknown adequate IOP control and prolonged standing corneal edema. Despite this challenge, 85% of patients had improved visual acuity, and none had a primary failure.

Although DMEK in patients with previous glaucoma surgery seems to have challenges, it should be performed by considering some critical steps and modifications. Graft survival is reduced not only in DMEK but in all other keratoplasty techniques. Therefore, these patients should be given the opportunity to undergo DMEK despite the risk of future re-grafting.

DMEK and Cataract Surgery

Although triple DMEK (simultaneous DMEK, cataract surgery, and IOL implantation) is often preferred in phakic patients, this procedure may lead to a refractive shift that is difficult to predict. Some recent studies have shown that a small hyperopic shift could be observed after DMEK.[66,67,68,69] Hence during IOL selection, these studies suggested a -0.50 to -1.0 D refractive target to provide emmetropia or slight myopia after DMEK. However, some individual cases showed large hyperopic and myopic shifts, particularly in advanced Fuchs endothelial dystrophy cases due to anterior curvature changes.[66] Apart from accurate IOL selection, endothelial cell density loss and DMEK graft detachment rate are other areas of concern in these cases.[70,71,72,73]

In recent studies, several approaches have been performed during triple DMEK. Laaser et al.[71] targeted -0.75 D refractive power for IOL selection. They did not find any adverse effect on endothelial cell function or graft adhesion due to the triple procedure. Schoenberg et al.[73] targeted a -0.50 D shift from IOL calculation due to +0.50 D hyperopic shift expectation after DMEK. The spherical equivalent median value was 0.0 D (range -0.25 to 0.25) postoperatively, and no astigmatic change was seen.

The average endothelial cell loss after 6 months was 26% to 40% in recent studies.[70,71,72] The difference was not significant between pseudophakic and triple DMEK eyes.[70,74] Better visual outcomes were seen in triple DMEK eyes. Although visual outcomes are promising, overhydration of the cornea and viscoelastic use during cataract surgery may interfere with graft attachment in triple DMEK.[70] Eliminating the use of viscoelastic during graft insertion is quite important. Another critical point is that the second eye's refractive shift may follow that of the first eye. Therefore, the first eye could be a reference point for the second eye's future surgery.[75]

The need for toric IOLs to neutralize corneal astigmatism could be a major concern in a triple procedure. Yokogawa et al.[76] evaluated 15 eyes of 10 patients with cataract extraction, toric IOL placement, and DMEK surgery for Fuchs corneal dystrophy. Keratoscopy measurements were obtained from Scheimpflug corneal imaging, and an online toric calculator was used to determine the cylinder power of the toric IOLs. The spherical

target varied between -0.50 and -1.00 D due to the mild mean hyperopic shift seen with DMEK surgery. Postoperatively, 61.5% of eyes gained uncorrected distance visual acuity better than 20/40 and mean best spectacle-corrected distance visual acuity (logMAR) increased from 0.21±0.15 to 0.08±0.12 ($p<0.01$). The refractive astigmatism was also significantly decreased from 2.23±1.10 D (range 0.75-4.25 D) to 0.87±0.75 D (range 0.00-3.00 D) postoperatively ($p<0.01$). In one eye, no improvement was observed due to rotational misalignment by 43 degrees. The prediction error of astigmatism at the corneal plane was 0.77±0.54 D (range 0.10-1.77 D). Four eyes with preoperative with-the-rule corneal astigmatism had postoperative against-the-rule refractive astigmatism. The authors emphasized the importance of rechecking the IOL alignment after DMEK graft placement to avoid clockwise rotation of the IOL.

In the absence of cataract, phacoemulsification may be delayed as a future option after DMEK.[77] However, if phacoemulsification after DMEK is required, its potential impact on graft function should be taken into account. Since DMEK grafts tend to adhere stronger to the recipient posterior stroma than "virgin" DM, manipulations during cataract surgery may not create a potential risk for DMEK graft dislocation.[78] Musa et al.[79] reviewed phacoemulsification outcomes after DMEK and did not show any graft dislocation or detachment in those eyes. The refractive outcome was mostly within ±0.50 D.[72,79,80] However, donor endothelial cell density decreased significantly in eyes with previous DMEK.[79] This study included high-risk eyes (e.g., multiple intraocular surgeries, advanced glaucoma). It was mentioned that DMEK graft endothelium resistance to trauma may not be as good as "virgin" endothelium.

A hyperopic shift due to DMEK is an expected result. Some specific adjustments may be required in the triple procedure. However, cataract surgery after DMEK is more predictable. Therefore, no particular nomograms are obligatory in this situation.

DMEK in Complex Anterior Segment Changes

Other than the standard indication of Fuchs endothelial dystrophy, DMEK can serve as a routine procedure in endothelial decompensation even in complex preoperative situations such as the presence of anterior synechia of the iris, large iris defects, iridocorneal-endothelial (ICE) syndrome, aphakia, subluxated posterior chamber IOL, AC IOL, phakic IOL, and acute corneal hydrops. The main objective in these situations is to reconstruct the iris and iris-lens diaphragm intraoperatively or preoperatively while treating the patients with DMEK. The graft size should be selected according to available space, e.g., eyes with anterior synechia may require a smaller graft diameter.[81]

Weller et al.[82] presented 24 complex eyes with endothelial decompensation. They performed DMEK in eyes with ICE syndrome, aphakia, subluxated posterior chamber (PC) IOL, and AC IOL. The eyes with ICE syndrome (3 eyes) had anterior synechia that interfered with the opening of the chamber angle, corectopia, and a shallow AC. Synechiolysis was required in two eyes with DMEK, and rebubbling was performed in two eyes. However, no graft failure developed in follow-up visits. In eyes with aphakia, stabilizing the iris-lens diaphragm by implanting a scleral sutured PC IOL was performed as the initial step. In eyes with IOL subluxation or AC IOLs, IOL explantation and implantation of a scleral sutured PC IOL or scleral suture-fixation of the existing IOL were applied. Further surgical procedures such as pupilloplasty or anterior vitrectomy were performed if necessary. DMEK was performed after a mean of 5±4 months. Four eyes required rebubbling but no graft failure was observed during postoperative examinations. The authors emphasized the importance of graft diameter in ICE syndrome depending on the extent of the synechia. Free retrocorneal surface is significant in the determination of graft diameter. Additionally, the authors suggested a two-step procedure for eyes with IOL problems to prevent graft dislocation in a destabilized AC.

In another study, eight eyes with either ICE (4 eyes) or posterior polymorphous corneal dystrophy (4 eyes) underwent DMEK.[83] Three of the eyes had goniosynechiolysis and one eye had iridoplasty with DMEK. BCVA increased in all of the eyes. No graft failure or graft rejection was observed during follow-up visits. DMEK only replaces the diseased central endothelium; however, it does not heal ICE syndrome or posterior polymorphous dystrophy. The pathological endothelial cells persist at the peripheral cornea after surgery. These cells may induce corneal decompensation in the future, although the graft border could be a mechanical barrier delaying migration from the periphery to the central cornea. Treatment of glaucoma in ICE syndrome may be challenging. Hohberger et al.[84] presented a case with micro bypass Xen Gel stent after DMEK. They concluded that microinvasive surgery after DMEK has less adverse effects and provides good IOP regulation.

Conclusion

Data from the Eye Bank Association of America shows that between 2004 and 2014, the rate of PK decreased to half (from 95% to 42%) and was replaced by lamellar keratoplasty techniques (5% to 55%).[85] The volume of EK procedures has been doubling every year since 2011.[85]

Fuchs endothelial dystrophy (47.7%) is the most common cause of endothelial failure, followed by corneal edema after cataract surgery (17.8%) that needs EK. DMEK offers significantly better graft survival of 98.7% in these eyes than DSAEK (78.4%) and PK (73.5%) in Fuchs endothelial dystrophy. PK results in eight-fold higher rejection rates compared to DMEK.[5]

For challenging cases like eyes with glaucoma, failed grafts, and vitrectomized eyes, DMEK still offers quick visual recovery, better graft survival, and lower rejection rates compared to traditional PK.

Although it has a learning curve, the literature on new techniques of DMEK is expanding tremendously, making it possible to perform DMEK in a variety of challenging situations.

This review summarized different approaches such as using different graft sizes (hemi-DMEK, quarter-DMEK), different graft folding techniques (endothelium-in delivery methods), new unfolding techniques (using a diaphragm in vitrectomized eyes), new positioning techniques (3/4-DMEK in eyes with glaucoma shunts), and double layers of DM in cases of failed PK. Hopefully, more standardized innovative modifications will enable cornea surgeons to treat endothelial dysfunction in almost any situation with confidence and great success.

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