Descemet membrane endothelial keratoplasty (DMEK) is the closest to the physiological replacement of endothelial cells. In the initial years, the technique was surgically challenging. Over the years, with better understanding and modifications in the surgical steps, the technique has evolved as an alternative to more popular procedure Descemet stripping endothelial keratoplasty. The article highlights the various preoperative, intraoperative, and postoperative nuances of DMEK. Additionally, it summarizes the various comparative and noncomparative studies on DMEK outcomes.

**Key words:** DMEK outcomes, preoperative, postoperative nuances

In the last few decades, keratoplasty has evolved from full-thickness corneal transplantation to selective corneal transplantation. The endothelial keratoplasty (EK) evolved from posterior lamellar keratoplasty to Descemet stripping endothelial keratoplasty (DSEK), Descemet stripping automated endothelial keratoplasty (DSAEK), UltraThin DSAEK, Descemet membrane endothelial keratoplasty (DMEK), and direct cultured endothelial cell injection therapy.\(^1\) Although direct cultured endothelial cell injection therapy is the most specific treatment for endothelial diseases, it needs a larger multicentric trial on human eyes to prove its efficacy and reproducibility.\(^2,3\) Currently, the most physiological way to replace diseased endothelium is DMEK. This review focuses on surgical nuances involved in DMEK and their outcomes.

### Relevance of DMEK in Current Scenario

Among various options to treat endothelial disorders, DSEK is more popular due to the simplicity of the surgical procedure, easier learning curve, more versatile applications, and nonrestriction of donor age criteria. DMEK allows for a nearly exact anatomical replacement of abnormal endothelial layer has an advantage of more predictable refractive outcomes and lesser risk of allograft rejection in view of lower antigenic load of the lamellar graft. Further, due to the characteristics of Descemet membrane (DM) roll and nature of the surgery, the technique has generated renewed interest in donors of older age. With these advantages of DMEK, it has become a procedure of choice in several indications for EK.

The current review addresses donor preparation techniques, recipient bed preparation techniques, donor insertion techniques, and the surgical outcomes observed so far in the literature.

### Methods of Literature Search

We performed a literature search on the Pubmed database on June 1, 2021 using the following keywords: DMEK, techniques, outcomes, complications using “AND” and “OR”. A total of 426 articles were available on search; however, we limited our search to full-text articles written in English. Case reports, comments, letters to the editor, articles written in other languages, and duplicate articles were excluded from the study. A total of 162 articles were finally selected to be included in the study based on the relevance and availability of articles. Relevance was assessed after reading the abstracts of the articles. To avoid selection bias in selecting articles three independent selectors were appointed.

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Cite this article as: Singh P, Sinha A, Nagpal R, Chaurasia S. Descemet membrane endothelial keratoplasty: Update on preoperative considerations, surgical techniques, and outcomes. Indian J Ophthalmol 2022;70:3222-38.
Preoperative Considerations for DMEK

Donor related
- Donor age is an important consideration when planning for DMEK. Younger donors produce tighter scrolls and can cause difficult unfolding of graft intraoperatively and subsequent endothelial cell loss. The older donors have a less tight scroll and often have a lesser tendency to scroll. These physiological characteristics can influence the unfolding of the DM roll during surgery. However, the functional outcomes are comparable between young and old donors. The minimum endothelial cell density criteria can vary from various eye banks. As per the standard operating procedures of eye banks in India, a donor cornea with a minimum endothelial cell density of over 2400 cells/mm² is considered suitable for DMEK.
- The diabetic status of the donor is believed to be an important parameter to look for while considering donor preparation. The literature suggests an adhesive interface between the posterior corneal stroma and DM in diabetics. This results in an increased incidence of graft tearing during graft preparation and subsequent graft failure. However, donor diabetes status did not result in increased rebubbling rate and postoperative increased endothelial cell loss at 6 months.

Recipient related
- The cornea should be relatively clear to allow sufficient visualization of graft in the anterior chamber and its manipulation. So, DMEK is not ideal for situations of corneal decompensation with severe corneal haze and scarring that precludes the anterior chamber view.
- The anterior segment biometry is another parameter that needs to be evaluated before surgery. It depends on the axial length, corneal diameter, and lens status of the patient. Biometry of the eye using diagnostic tools such as anterior segment optical coherence tomography (OCT) and optical biometry devices helps in deciding the appropriate size and shape of graft depending on the availability of space. In general, the graft size is 2-3 mm smaller than the horizontal corneal diameter. Corneas with increased keratometry readings may need a larger size of the graft because of the increased posterior corneal surface area.
- Preoperative assessment for DMEK in PKP graft includes the use of modalities like anterior segment optical coherence tomography to assess the graft-host junction, undesired posterior morphological changes, or peripheral anterior synechiae.

Surgical Steps of DMEK

The surgery involves DM roll preparation, graft insertion, unfolding the graft, and its attachment with air bubble tamponade. Fig. 1 illustrates several surgical steps of the surgery.

DMEK donor tissue preparation
There are various techniques described for endothelial graft preparation with no consensus on a uniform standard method. Broadly the techniques for donor tissue preparation can be categorized into manual peeling or techniques aiming at achieving detachment between DM and posterior stroma by using either air or fluid utilizing the similar concepts of anterior lamellar keratoplasty. The donor tissue preparation techniques along with advantages and disadvantages have been summarized in Table 1.

Recipient bed preparation
For a recipient bed preparation, a correct estimate of the anterior chamber dimension is needed. Depending on the available free posterior corneal surface, a rough estimate of the recipient bed size is made. The corneal tunnel configuration and extent are subsequently decided based on the recipient bed size.

Kruse et al. in their study, used a 9-mm trephine mark on the anterior corneal surface to guide the recipient bed size. Tunnel at 12 O’clock with paracentesis at 3, 11, and 1 O’clock was suggested in this study. The descemetorhexis was done through the paracentesis under air with an inverted hook. Güell et al. also suggested descemetorhexis under air with reversed Sinskey hook via superior 2.4 mm corneal tunnel.

The paracentesis was made at 3 and 9 O’clock positions in this study. Owing to the better visualization under air descemetorhexis has been advocated to be done under air in most of the available literature. In a study by Takahiko Hayashi et al., the author proposed a standard technique for descemetorhexis; however, the author used Hayashi DMEK stripping forceps to remove the DM from the anterior chamber. The literature search also revealed the use of viscoelastic for descemetorhexis. The author also advised roughening of peripheral 2 mm of the bare stroma with the scraper to facilitate better graft adherence. In cases with endoglide-assisted insertion of graft, a temporal scleral tunnel making is preferred with a nasal paracentesis for endoglide placement forceps to pull the graft into the anterior chamber.

Donor Insertion Techniques and Devices

There are various considerations while inserting the donor graft inside the anterior chamber. Among the various technical nuances during insertion of DMEK graft, maintenance of anterior chamber depth, the donor graft orientation, and method of delivery of graft are important. The literature suggests different methods to facilitate smoother graft insertion with minimal damage to endothelial cells.

Graft delivery techniques and devices
Kruse et al. used an injector cartridge used for intraocular lens implantation for graft loading and insertion into the anterior chamber. For graft loading, the author used a pre-fluid-filled cartridge such that the graft roll floats into the cartridge. The injector is inserted into the anterior chamber and the graft injected.

Güell et al. also used a 1.8-mm prefilled cartridge for graft loading and injection; however, they suggested the use of a small air bubble at the rear end of the DM scroll. Price et al. also used an intraocular lenses (IOL) cartridge for graft insertion in their study; however, for graft loading, the Tan forceps were used. In another study using IOL cartridge, flushing was compared with the pushing technique of DMEK graft insertion revealing prolonged insertion to attachment time when the graft is flushed. However, it did not affect the outcome.

Dapena et al. in their study used a no-touch technique with a customized glass pipette or a Pasteur glass pipette for loading and delivery of graft into the anterior chamber. The author postulated that the glass surface unlike plastic cartridges is
smooth and less traumatic and can be made without sharp
ces. However, the small entry port causes friction trauma
and, thus, potentially more damage to the endothelial cells.
Melle's glass injector offered a less traumatic graft loading
because of the large lumen for entry; however, the assembly
and disassembly of the glass injector are cumbersome. In an
attempt to overcome the friction-related trauma during graft
loading and cumbersome maneuvers in loading and injecting
the graft, FA Montiel suggested the use of an asymmetric
double port injector. All these injectors seemed expensive and
supposedly did not have a closed system, causing inadequate
fluid control and an increased risk of contact of graft tissue
with the wall of the injector. Kim et al. proposed the use of a
relatively inexpensive and effective injector with a closed
system to facilitate adequate fluid flow around the graft tissue.
The author used the cut end of intravenous tubing mounted
over prefilled syringe with the Alcon IOL B cartridge at the
proximal end. The outcomes were comparable with larger
series where a glass injector has been used. In a similar study
by Mehrnaz Ighani et al., the author used the Bonfadini–Todd
injector (comprised of Alcon B cartridge, plastic tubing, and
syringe) for graft insertion. The technique described is not only
inexpensive but also gives equally good surgical outcomes.

In a multicenter study, the author noted a higher
postoperative graft detachment rate in cases where plastic
graft inserters were used compared to glass inserters. A high
detachment rate has been attributed to more endothelial cell
damage, possibly due to graft touch inside the inserter due to
electrostatic charges.

In another study by Marcus Ang et al., the author advised
the use of endoglide and the D-Mat-assisted DMEK graft
delivery system. The development of this device potentially
decreases the endothelial loss occurring during graft insertion.
A similar study by Tan et al. suggests lesser endothelial
damage with endoglide-assisted DMEK with promising clinical
outcomes. Hybrid DMEK by the pull-through technique is a
modification of the above-described technique with the use of
stroma in place of D-Mat. The author emphasizes that the
endothelium-in configuration during insertion decreases cell
loss; however, another study comparing endothelium-in with
endothelium-out insertion of DMEK graft revealed similar

Figure 1: Showing DMEK surgical steps. (a) Peripheral lifting of DM–endothelial complex using sinsky hook. (b) DM–endothelial complex
peeling. (c) DM scroll. (d) Loading of DM scroll. (e) Injection of DM scroll into the anterior chamber. (f) DM scroll in AC. (g) Unfolded DM scroll in
the anterior chamber. (h) DM scroll fastened to the posterior corneal surface using an air bubble. (i) Post-DMEK at 1-week follow-up
## Table 1: Donor preparation techniques and advantages and disadvantages of each procedure

| Techniques                  | Basic principle                                      | Modifications                                                                 | Advantages                                      | Disadvantages                                                                 |
|-----------------------------|------------------------------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------------------------------------|
| A. Manual peeling           |                                                      |                                                                               |                                                 |                                                                                |
| 1. Melles et al.            | Superficial trephination                             | Rectangular cuts instead of trephine cuts gave the advantage of a long flat edge to grasp and peel the DM smoothly | Endothelial damage at the site of grasping      |                                                                                 |
|                             | BSS immersed donor tissue                           |                                                                               | Donor tissue with >2 mm scleral rim to mount on artificial anterior chamber     |                                                                                 |
|                             | Single-handed DM peeling                             |                                                                               | 8/48 had tearing                              |                                                                                |
|                             |                                                      |                                                                               | The size of DM preparation is limited by the length of platform forceps         |                                                                                |
| 2. Zhu et al.               | Tissue mounted on the artificial anterior chamber with the endothelial side up | Rectangular cuts instead of trephine cuts gave the advantage of a long flat edge to grasp and peel the DM smoothly | Endothelial damage at the site of grasping      |                                                                                 |
|                             | No underwater system                                |                                                                               | Donor tissue with >2 mm scleral rim to mount on artificial anterior chamber     |                                                                                 |
|                             | 4 incisions on DM DM peeling in a rectangular fashion| Rectangular cuts instead of trephine cuts gave the advantage of a long flat edge to grasp and peel the DM smoothly | Endothelial damage at the site of grasping      |                                                                                 |
|                             |                                                      |                                                                               | No new instrument                            |                                                                                |
|                             |                                                      |                                                                               | Endothelial loss <3%                         |                                                                                |
| 3. Lie et al.               | 180-degree loosening of DM from the scleral spur    | Acceptable ECL                                                                | Linear streaks reflecting disrupted endothelial cell junctions which restored  | Focal ECL during forceps manipulation                                            |
| 4. Groeneveld ‑Van‑ Beek    | 360-degree DM and adjacent TM loosening             | No‑touch technique                                                            | Focal ECL during forceps manipulation          |                                                                                |
|                             | Trephination on ‑6 D contact lens                    | Stripping DM with a peripheral rim of TM facilitate thin graft handling        | Focal ECL during forceps manipulation          |                                                                                |
|                             |                                                      | No damage to the stromal bed and hence useful for DALK                         | Focal ECL during forceps manipulation          |                                                                                |
| 5. Giebel et al. (SCUBA     | DM stripping in viewing chamber                      | Better tissue visualization                                                    | 12/72 DM tear                                 |                                                                                |
| technique)                  | Tissue submerged in storage solution                 | Easier to rescue in case of tears                                              |                                                |                                                                                |
| 6. Tenkman LR               | Y Hook for scoring to produce a smooth break         | Edge lifting was guided by the concept of progressing from areas of minimum    | HST 13%                                        |                                                                                |
|                             | Blunt micro finger for 360-degree edge lift: Glide  | tension (peaks) to areas of maximum tension (craters)                         |                                                |                                                                                |
|                             | technique 4 quadrant “Corridor method” of DM peeling | - Corridor method helped to minimize tension during peeling                    |                                                |                                                                                |
|                             | using Tubingen forceps                              | - Corridor method helped to minimize tension during peeling                    |                                                |                                                                                |
| 7. Kruse et al.             | 2 forceps technique to lift DM similar to lifting a  | Scratching the DM outside prevented the EDM from tearing inside                 | Increased preparation time (decreased from 1.5 h to with experience)             |                                                                                |
|                             | tablecloth                                           | 2 Forcep technique decreased the surface tension                              |                                                |                                                                                |
|                             | Razor blade to scratch peripheral DM and edge lift   | Reproducible                                                                   |                                                |                                                                                |
|                             | with round blade                                     | Minimal tearing                                                                |                                                |                                                                                |
|                             | Orientation mark with 1 mm trephine                  |                                                                                            |                                                |                                                                                |
| 8. Yoeruek et al.           | 2 novel untoothed forceps for DM peeling              | Faster                                                                         | Novel instruments                              |                                                                                |
|                             | - Curvilinear 8 mm dissection forceps and mmicro     | Lower endothelial cell loss                                                    | Study used old donor tissue                   |                                                                                |
|                             | tears forceps                                        | 8 mm dissection forceps allowed immediate preparation of membrane with        |                                                |                                                                                |
|                             |                                                      | minimal grasping rate                                                         |                                                |                                                                                |
|                             |                                                      | Microtear forceps increased tissue salvage                                    |                                                |                                                                                |
| 9. Sikder et al.            | 400‑µ head microkeratome to remove the majority of    | - Thin rim of posterior residual stroma permits easy donor button trephination and tissue | Possible perforation during manual removal of stroma |                                                                                |

Contd...
| Techniques | Basic principle | Modifications | Advantages | Disadvantages |
|------------|----------------|---------------|------------|---------------|
| **stroma** | Manual dissection of residual stroma | - Microtears used as a hinge for DM peeling | - Cost-effective | Overall 76% success rate (increased from 72% in first 25 cases to 80% in next 25 cases, prepared by eye bank technicians) DM tear (10%) Severe cell loss (14%) in cases with difficulty in remounting the tissue and incomplete DM edge stain |
| 10. Tausif et al. | | | - Relatively easy assessment of endothelial integrity before trephination | |
| 11. Maharana et al. (SHARP technique) | Sinskey hook for freeing DM edge Bimanual DM peeling | Simple | Easy | Success rate 86.6% (13/15) Complete success in 66.6% and partial success in 20% |
| 12. Tzamalis et al. (Yogurt technique) | Novel DMEK punch (100 µ guarded blade and missing 1 Clock hour) to create an uncut hinge Single-peel technique | DM is stripped easily from its a natural end point, that is, Schwalbe’s line | Reproducible Low failure rate independent of surgeon’s experience level | Specially designed punch |
| **B. Pneumatic dissection** | | | | |
| 13. Ignacio et al. | Air injection to achieve detachment between DM and posterior stroma - 9-mm trephination and air injection in the artificial anterior chamber | | | Rare chance of failure to obtain big bubble (1/20) |
| 14. Busin et al. | Anterior stroma removed with 300-µ head microkeratome before air injection Residual donor tissue placed endothelial side up and 30 G needle used to inject air | The dissected sclerocorneal rim can be stored There is no rolling of tissue and hence peripheral ECL is prevented Easy transfer of tissue from preparation site to insertion site Touch-free technique Less ECL No added skill is required to master the technique | | |
| 15. Venzano et al. | Applied Anwar air bubble technique Trypan blue stained endothelium to facilitate proper positioning of the air injection needle Hypotony before air injection | Depth of needle and adequate hypotony helped in successful DM separation | | A pilot study with small sample size |
## Table 1: Contd...

### Summary of donor preparation techniques

| Techniques | Basic principle | Modifications | Advantages | Disadvantages |
|------------|----------------|---------------|------------|---------------|
| 16. Zarei Ghanavati et al. (Reverse big bubble technique) | Tissue mounted endothelial side up with air injection in the posterior stroma Older tissue with high endothelial cell count preferred | Better visualization with the endothelial side up Faster, easier, and without endothelial touch during detachment as compared to manual dissection Short learning curve | Younger donor tissue resulted in 1 DM rupture and 1 incomplete detachment out of 10 cases |
| 17. Studeny et al. (DMEK-S) | Big bubble achieved with donor tissue mounted endothelial side up Central 6 mm DM endothelial complex with surrounding 1 mm wide 100-µ thick stromal rim | Easy tissue handling due to presence of stromal rim No special instrument | - Larger width of tunnel incision (4.75 vs 3.50)( but still sutureless) - Rate of loss of donor cornea due to bubble rupture (decreased from 10 to 5% with experience ) |
| 18. Agarwal et al. (PDEK) | PDL, DM, and endothelium transplanted Donor tissue mounted endothelial side up 30 G needle used to obtain Type I Bubble Trypan blue used to stain the tissue | Easier tissue handling due to PDL Less haze due to less keratocytes Allowed use of younger donor tissue<50 years | Mean graft diameter is lesser than usual DMEK graft and hence fewer endothelial cells are transplanted (compensated with less ECL during preparation and younger donor tissue use) Chances of creation of type 2 bubble instead of type 1 bubble |
| C. Hydrodissection | Fluid injection to achieve detachment between DM and posterior stroma | DM sectioned 330 degree Endothelium detached from nontrephined zone to create a liftable flap 27 G cannula used to inject fluid | Simple Less ECL The endothelium is rolled in | 4% Graft loss (seen in younger donors) |
| 19. Muraine et al. | Donor tissue immersed in organ culture media 25 G needle to inject fluid Anterior stroma trephined after mounting donor tissue on custom-made artificial chamber with the epithelial side up | Standardized, no-touch, ready to use tissue Reduced preparation time The graft can be preserved in deturgescent medium for up to 7 days | Bubble burst due to liquid overfilling in 5 out of 30 cases Average ECL postpreservation 27.69% |
| 20. Salavalaio et al. (Sub Hys) | Donor tissue placed endothelial side up Trypan blue injected to obtain DM detachment after negating 2 mm area of strong DM adhesion The first technique to describe selective staining of the stromal side of DM | Rapid and easy Highly reproducible No special equipment needed Minimal tissue manipulation Selective staining of the stromal side of DM, thus, avoiding direct contact with endothelial cells and producing a homogenous stain Rescue technique in case of tearing or strong adhesions | 1/86: central tear |
outcomes with either of the techniques.\[51\] In another ex vivo study by Chong et al.,\[48\] greater endothelial cell viability was noted with the endothelium-in technique compared to the endothelium-out technique. The timing of preloading of the graft into the device is having a significant bearing on the scrolling tendency of the DMEK graft. If preloaded 48 h before the surgery, the graft scrolling tendency decreases for 2 min and gives sufficient time to the surgeon to fix the graft before it recurls.\[49\]

A novel technique of donor insertion described by Fogla et al.,\[40\] uses a glass cartridge attached to the prefilled syringe. The cartridge is inserted into the AC and rotated to orient the graft in the desired orientation. The AC maintainer is switched off and disconnected from the intravenous tubing followed by graft injection. The absence of fluid counterpressure facilitates a smooth delivery of graft in the correct orientation.

In another technique for the graft insertion, the infusion cannula is directed to the internal lumen of the cartridge from the opposite paracentesis. This draws the graft into the anterior chamber with a no-touch technique.\[50\]

**Graft unfolding and attachment techniques**

The various techniques can be used either as standalone or in various combinations depending upon the clinical situation and the expertise of the surgeon. Liarakos et al.\[51\] retrospectively evaluated various techniques for the unfolding of DMEK graft in their 100 consecutive cases and found no correlation between the technique chosen to unfold the graft and postoperative outcomes in terms of visual acuity, endothelial cell counts, and complication rates. The technique employed to unroll a graft inside the anterior chamber depends on factors such as the orientation of the double Descemet roll-formed, the tightness of the folds, and whether the two halves are symmetrically folded or not.

**A) Successful formation of a symmetric double Descemet roll**

*Standard No‑Touch technique*[52]

The formation of a double Descemet roll is the most essential part of this technique. The formation of the Descemet roll is ensured by irrigating the Descemet roll using the balanced salt solution so that the graft opens and folds back on itself forming two adjacent rolls. Following graft injection into the anterior chamber, the position of the folds is checked by the Moutsouris sign. In case the graft is oriented correctly with the curls of the double roll facing upwards, the tip of the cannula positioned inside a peripheral curl appears blue due to the overlying blue-colored donor tissue suggestive of a positive Moutsouris sign. However, if the graft is positioned with edges facing downwards, the tip does not change its color since it is not able to find the curls. This is referred to as the negative Moutsouris sign.\[51,52\]

The first separation of the graft is achieved by gently tapping the outer cornea followed by injection of an air bubble between the rolls and then subsequently enlarging it. Air bubble aims to secure the graft in its upright position and allow for its centration. The bubble is enlarged to fixate the graft onto the iris, while the peripheral part of the graft is being opened. Once the graft is completely opened up, the air bubble lies in the interface between the graft and the cornea is aspirated and injected beneath the graft to secure it onto the host stroma.

**B) Symmetric double Descemet roll is not formed**

*a. Dirisamer technique*

The technique is employed in case an asymmetric double roll is formed, consisting of a small flange adjacent to the larger body of the Descemet roll. It utilizes 2 cannulas, one to stabilize the relatively less folded part of the graft by gently pressing over the corneal surface and the second to unfold the tightly rolled part of the Descemet roll.\[51\]

*b) Dapena maneuver*

This technique involves positioning a small air bubble over a partially unfolded graft. The graft is unfolded by manipulating the air bubble from the outer corneal surface using a blunt cannula. The presence of an air bubble acts as an intraocular tool and helps in unrolling the flanges of the graft.\[53\]

*c) Single‑sliding cannula maneuver*

Loose Descemet rolls wherein the graft has a tendency to unfold on its own are better suited for this technique. This method involves the application of repetitive sliding movements over the anterior corneal surface, keeping the cannula parallel to the Descemet roll in a centrifugal manner.\[51\]

**C) Double Descemet roll placed in an upside-down manner: “Flushing”**

In case the double roll is oriented in an inverted manner after injecting inside the anterior chamber, as confirmed by a negative Moutsouris sign, the graft is repositioned by gentle flushing using the balanced salt solution, injected from one of the side ports.\[51\]

**D) Persistent small folds in an otherwise completely opened Descemet’s roll: “Bubble Bumping”**

Once the Descemet roll is completely opened up, small, localized undulations or inward folds may interfere with the complete apposition of the graft with the posterior stroma. Gentle taps applied over the anterior corneal surface localized to the area of inwards folds help to completely open up the graft.\[51\]

**Techniques to know correct orientation of DMEK graft within the anterior chamber**

- a. Moutsouris sign/the “Blue Cannula” tip sign [Dapena I et al.][51]
- b. Stamped DMEK grafts [Veldman et al.]
- c. Placement of a single peripheral triangular mark [Rickmann et al.]
- d. Use of paired asymmetric marks [Matsuzawa et al.][55]
- e. Peripheral graft staining/“Ghost DMEK” technique [Livny et al.][56]
- f. Kobayashi or the K sign (endo‑illuminator assisted) [Kobayashi et al.]
- g. Use of intraoperative ultrasound biomicroscopy [Nahum Y et al.][58]
- h. Microscope integrated OCT‑aided visualization [Steven P et al.][59,61]

**Complications and Management**

The complications of DMEK have been enumerated along with various predisposing factors and management in Table 2.\[10,84,109,113‑116]

- a. **Graft detachment:** \[110,12,93,53,79,40,62‑84]
- b. **Raised IOP:** \[10,19,62,66,85‑94]
- c. **Graft rejection:** \[92‑112]
- d. **Graft failure:** \[10,84,109,113‑116]
- e. **Pupillary abnormality:** \[117‑119\]
| Complications | Risk factors | Management |
|---------------|--------------|------------|
| **1. Graft detachment** | Host Factors:  
Incomplete DM removal  
Smaller descemetorhexis  
Improper graft orientation  
Posterior vitreous pressure  
Postoperative ocular hypotony  
Donor Factors (conflicting evidence)  
Donor tissue age  
Storage medium  
In some studies, younger donors and tighter rolls and tissue stored in cold storage had a higher detachment rate as compared to organ culture storage  
Surgeon inexperience | Staining for proper visualization of DM and careful intraoperative inspection under air to ensure complete DM stripping  
Avoid the use of plastic or viscoelastic material  
Larger descemetorhexis  
Femtosecond-enabled descemetorhexis produces a smooth interface  
Marking the graft, checking the orientation with Moutsouris sign or intraoperative OCT  
Intraoperative soft eye by ocular massage or applying Honan balloon for 10 min, avoiding tight eyelid speculum and maintaining antitrendelenburg position  
Consider prolonged postoperative air tamponade for at least 1 h or use gas which persists longer in the eye, especially in aphakic or vitrectomized eyes or eyes with glaucoma shunts  
Rebubbling with 100% air or 12–14% C3F8 or 20% SF6 for detachments which are complete or central and for peripheral detachments involving >1/3rd graft surface area following an AS-OCT based algorithm performed at 1 h, 1 week, and 1 month  
Repeat transplant  
Refinement in technique and surgeon experience |
| **2. Raised IOP** | Exacerbation of preexisting glaucoma  
Preoperative raised IOP  
Angle supported phakic IOL  
De-novo glaucoma  
Air bubble-induced mechanical angle closure  
Steroid response  
PAS | Close IOP monitoring in patients with risk factors  
Reducing residual post-op air bubble  
Inferior PI  
Air release and dilatation  
Switch to low-potency steroids  
Avoid DMEK graft decentration to prevent PAS formation |
| **3. Graft rejection** | Ethnicity: Asians have a stronger immune response than Caucasians  
Noncompliance to topical steroids | Routine follow-up to detect subtle findings of asymptomatic endothelial rejection  
Resumption of topical steroids |
| **4. Graft failure** | Primary:  
Intraoperative graft manipulation  
Subclinical pre-op endothelial dysfunction  
Inverted graft transplantation  
Storage of precut tissue in deswelling medium with dextran and insufficient rinsing of media remnants before insertion  
Secondary:  
Endothelial failure – patients with glaucoma/postsecond rebubbling  
Graft rejection  
Graft survival FECD >BK | Careful screening in eye banks to rule out subtle endothelial changes as in pseudoexfoliation syndrome  
Less intraoperative manipulation and correct graft orientation  
Repeat DMEK |
| **5. Pupillary abnormality** | An acute increase in IOP, especially in the first 24 h, leads to iris ischemia with sphincter muscle dysfunction  
Air tamponade >70%  
Intraoperative pupillary dilatation along with longer retention of SF6  
Shallow AC  
Triple procedures have increased risk of synechiae  
Learning curve | Use of air over SF6  
Early synechiolysis  
Surgeon experience |
| **6. Cystoid macular edema** | DMEK combined with cataract surgery  
Short AL  
Longer duration of surgery  
Iris manipulation  
Predisposing risk factors like contralateral CME, PG analog use, ERM, DR, macular degeneration, previous retinal surgery, RVO, VMT | Intensive topical corticosteroids in the first week of DMEK with cataract surgery  
Minimal iris manipulation |
| **7. Cataract** | Age  
Iatrogenic injury to the anterior lens capsule  
Increased duration of air and lens contact | Intraoperative pupil constriction  
Decrease the air bubble to 30% at the end of the surgery  
Cataract surgery for clinically significant cataract |

*Contd...*
8. IOL calcification

Inflammatory reaction with disrupted blood–aqueous barrier
Metabolic changes in aqueous humor
Dehydrated hydrophilic acrylate in contact with air leads to deposition of hydroxyapatite on the IOL surface
Calcification of hydrophilic IOL and hydrophilic IOL with hydrophobic coating has also been reported

Management

Symptomatic IOL opacification needs IOL explantation

Table 2: Contd...

f. Cystoid macular edema,[10,67,89,93,116,120,123]
g. Cataract,[124-126]
h. IOL calcification.[127-135]

Outcomes of DMEK in Various Clinical Scenarios

Since the first published report of preliminary clinical results of DMEK by Melles G et al. in 2008,[65] corneal surgeons across the world were motivated to adopt this new technique of selective endothelial layer transplantation. In a nonrandomized study involving 10 patients with either Fuchs endothelial corneal dystrophy (FECD) or pseudophakic bullous keratopathy (PBK), DMEK was performed using DM rolls prepared from organ-cultured donor corneal scleral rims. At 1 month postoperatively, 6 out of 10 eyes achieved a best-corrected visual acuity (BCVA) of 20/40 or better of which 3 eyes reached 20/20. The observation of such a quick and nearly complete visual recovery as compared to the previously described posterior lamellar transplantation techniques such as descemetoctomy (DLEK) and DMEK made the authors conclude that the surgical procedure might have a potential to surpass other well-accepted methods of endothelial transplantation. This observation of early visual recovery following DMEK was further strengthened in a subsequent larger nonrandomized study by the same authors involving 35 patients with FECD and PBK.[136] In most cases, functional visual improvement was obtained within 1–3 months. The long-term sustainability and predictability of DMEK were further proved in a subsequent study, wherein a subset of patients was followed up to 24-month postoperative period. A 25% rate of endothelial cell loss was noted in the early postoperative phase (1–2 years), which was quite similar to that reported with other techniques of EK.[137] In a prospective, multicentric trial by Price et al.,[138] the results of DMEK were evaluated in 60 eyes with FECD, PBK, and failed graft. The median best spectacle-corrected visual acuity (BSCVA) at 1 month was 20/30 with 94% eyes achieving 20/40 or better at 3 months. The endothelial cell loss was 30 ± 20% at 3 months follow-up and 32 ± 20% at 6 months, consistent with the previous reports of DMEK. The main complication observed was partial graft detachment, occurring in 63% of eyes predominantly clustered in the first 2 weeks.

Further studies evaluating long-term outcomes of DMEK over 3 and 5 years[139] reported a cell loss of 42 and 55%, respectively. A biphasic pattern of endothelial cell loss was observed with a sharp decline of 20–29% in the first 6 months followed by a slow decline of approximately 10% per year. The pattern of endothelial cell loss observed was found to be similar to that seen after other forms of endothelial keratoplasties.

The favorable outcomes of DMEK in initial studies in terms of “quick” and “nearly complete” visual recovery substantiated the concept that thinner grafts help to achieve better visual outcomes.[132] In today’s date, the literature is replete with both comparative and noncomparative studies, evaluating the outcomes of DMEK in comparison with other forms of endothelial transplantation such as DSAEK and ultrathin DSAEK and as a standalone procedure in various clinical scenarios. Over a while newer advancements have been incorporated such as the use of intraoperative OCT[54,59] to help in intraoperative and postoperative decision making and the use of femtosecond laser for assisting descemetoctomy.[141]

a) Changes in corneal biomechanical and optical properties after DMEK

DMEK allows near-normal visual, anatomical as well as ultrastructural rehabilitation without altering the biomechanical properties of the cornea. Shilova NF et al.[142] evaluated the biomechanical properties of DMEK-operated PBK eyes with normal fellow eyes, using an ocular response analyzer. The operated and normal fellow eyes were comparable in terms of mean values of corneal hysteresis and the corneal resistance factor.

In a comparative study by Rudolph M et al.[143] corneal higher-order aberrations were evaluated in eyes undergoing DMEK, DSAEK, penetrating keratoplasty (PK), and in unoperated control eyes. Compared to PK and DSAEK, DMEK eyes showed significantly lower values of mean higher-order aberrations for the central 4-mm zone of the posterior corneal surface. This was accompanied by a significantly better BSCVA in DMEK eyes compared to both DSAEK and PK. These findings were attributed to the minimal alteration of the posterior corneal surface and attainment of a near-normal corneal anatomy, in eyes undergoing DMEK.

b) DMEK in eyes with FECD [Fig. 2]

The first series of DMEK performed in patients with FECD was reported by Ham L et al.[144] in 2009. This nonrandomized study reported the outcomes of DMEK performed in 50 consecutive cases of FECD. Of the 50 eyes, 10 experienced graft failure, predominantly due to graft detachment; either partial or complete, requiring secondary DSEK. In the remaining 40 eyes, 95% attained a BCVA of 20/40 with 75% of them reaching up to 20/25, at 6 month follow-up. The overall visual recovery was found to be comparable to PK and other techniques of EK such as DLEK and DSEK/DSAEK with the
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added advantage of nearly complete visual recovery in the majority of patients within 1–3 months. The endothelial cell loss at 6 months was approximately 30%, with cell counts averaging around 1876 ± 522 cells/mm², comparable to other forms of keratoplasties.

Zwingelberg SB et al. reported the long-term outcomes of DMEK performed in a large study comprising of 402 eyes, including 371 eyes with FECD and 31 eyes with PBK. Three years following DMEK, a significant decline was noted in the central corneal thickness with no change in the peripheral corneal thickness. The BSCVA was comparable among the two groups at 3 years follow-up.

Cabrerozo J et al. evaluated following DMEK in eyes with bilateral FECD, in terms of color vision and contrast sensitivity, and overall patient satisfaction. Results were compared between the untreated FECD-affected eye and the DMEK-treated FECD eye. Following DMEK, a significant improvement in contrast sensitivity was noticed besides improvement in the BSCVA. Comparing phakic and pseudophakic eyes, phakic eyes performed better in terms of improvement in contrast sensitivity. Color vision was, however, comparable among the treated and the untreated groups.

c) Outcomes of DMEK in phakic eyes

Removing or retaining the crystalline lens has been a matter of debate among corneal surgeons while performing EK. The observation is that most patients which are planned for EK have some degree of cataract which may be aggravated by intraocular surgery and use of postoperative corticosteroids. Another clinical observation has been that phakic eyes have been seen to perform better compared to pseudophakic eyes, following EK. Loss of accommodation, posterior capsule opacification, and changes in the optical properties of the lens system are factors that contribute to the degradation of visual

Figure 2: Representative slit-lamp photographs (a and b), OCT images (c and d), specular microscopy (e and f) of the right and left eye of 8 year follow-up after DMEK triple. The patient had Fuchs endothelial dystrophy. At the 8 year follow-up, the endothelial imaging shows an endothelial cell loss (ECL) of 53 and 50% from baseline donor. Endothelial cell density (EDC) in the right and left eye, respectively.
quality in pseudophakic eyes. In a study by Parker J et al.,[124] the outcomes of DMEK performed in phakic eyes with FECD were compared with age-matched pseudophakic patients. Visual acuity equal to or better than 20/13 was observed only in phakic eyes, suggesting better optical quality with the crystalline lens in situ. Both groups were similar in terms of complication rates.

d) Outcomes of DMEK combined with phacoemulsification and IOL implantation (DMEK triple procedure)

Studies reporting the outcomes of DMEK combined with cataract surgery in eyes with FECD and preexisting cataracts have shown predictable and stable refractive results without any added risks of postoperative complications, compared to DMEK alone.[89,147,148] In eyes with significant cataracts, performing cataract surgery along with replacing the diseased endothelium offers faster visual rehabilitation and cut shortens the costs and risks associated with a second intraocular procedure. Chaurasia et al.[89] compared the clinical outcomes of DMEK single versus triple procedure in a retrospective study involving 492 eyes with either FECD, secondary corneal edema, or a prior failed EK. The authors observed similar rates of air re-injection and median endothelial cell loss (26%) in both groups.

Table 3: Summary of comparative as well as noncomparative studies reporting the outcomes of DMEK in various clinical scenarios

| Author/Year       | n   | Study design | Indication     | Intervention | Outcome                                                                 |
|-------------------|-----|--------------|----------------|--------------|-------------------------------------------------------------------------|
| Zwinkelberg SB et al./2021 | 402 | R            | FECD (n=371) PBK (n=31) | DMEK         | At 3-year follow-up, BSCVA improvement in FECD and PBK eyes was comparable |
| Cabrerozo J et al./2014 | 29  | R            | Bilateral FECD | Unilateral DMEK | DMEK eyes had significantly better visual acuity and contrast sensitivity compared to the untreated FECD eyes. The color vision was, however, comparable among the two groups. Subjective optical quality was better in DMEK-operated eyes compared to fellow untreated eyes both in phakic eyes as well as in pseudophakic eyes. |
| Parker J et al./2012[124] | 99  | P Comparative | FECD          | DMEK         | Phakic and pseudophakic eye groups were comparable in terms of final visual outcome, visual rehabilitation rate, ECD, and complication rate at 6 months follow-up. |
| Shilova NF et al./2019[142] | 40  | R Comparative | PBK           | DMEK         | The mean CH and mean CRF values did not show any statistically significant difference between the DMEK and the normal fellow eyes. Mean CCT was smaller in the operated eyes compared to the fellow eyes. However, the CCT value did not show any correlation with either the CH or the CRF values. |
| Dunker SL et al./2020 | 54  | RCT          | FECD          | DMEK (n=29) vs UT-DSAEK (n=25) | Comparable mean BSCVA, endothelial cell density, and hyperopic shift noted at 12 months follow-up. DMEK group had a significantly higher percentage of eyes with 20/25 Snellen acuity |
| Mencucci R et al./2020 | 18  | R            | FECD          | DMEK vs UT-DSAEK (fellow eye comparison) | Comparable BSCVA noted at 12 months follow-up. Total and posterior corneal higher-order aberrations, posterior astigmatism, and total coma was significantly lower in eyes following DMEK. Visual acuity in both groups was found to significantly correlate mainly with anterior corneal aberrations. DMEK eyes performed better in terms of contrast sensitivity, posterior corneal aberrations, and overall patient satisfaction. |
| Romano V et al./2020 | 56  | R            | FECD and PBK  | Preloaded UT-DSAEK (n=31) vs preloaded DMEK (n=25) | At 12 months, logMAR BSCVA was significantly better in eyes undergoing Preloaded DMEK, compared with PI-UTDSAEK. (0.37±0.37 LogMAR, P<0.01). The percentage of people that achieved ≥20/30 was significantly higher in the preloaded DMEK group. The rate of rebubbling, however, was significantly higher for the same group. |
| Duggan MJ et al./2019 | 50  | RCT          | FECD and PBK  | UT-DSAEK (n=25) vs DMEK (25) | At 12 month follow-up, DMEK eyes had significantly lesser posterior corneal surface and total higher-order aberrations. Compared to baseline, UT-DSAEK eyes experienced an increase in total posterior HOAs at 12 months follow-up, while it was reversed for the DMEK eyes. |
| Ang MJ et al./2019 | 50  | RCT          | FECD and PBK  | UT-DSAEK and DMEK | Improvement in vision-related quality of life was found to be comparable among the two groups. DMEK eyes had significantly better visual acuity at 3, 6, and 12 months follow up. Endothelial cell counts and complication rates were similar till 12 months follow-up. |

Footnote: N – Total number of eyes enrolled, R – Retrospective, DMEK – Descemet membrane endothelial keratoplasty, UT-DSAEK – Ultrathin Descemet stripping automated endothelial keratoplasty, CH – Corneal hysteresis, CRF – Corneal resistance factor, Fuchs endothelial corneal dystrophy, BSCVA – Best spectacle-corrected visual acuity, PBK – Pseudophakic Bullous Keratopathy, ECD – Endothelial cell density, DMEK – Descemet membrane endothelial keratoplasty.
at 6 months follow-up. Ensuring complete removal of viscoelastic substance before initiating descemetorhexis and a well-placed IOL were considered important factors determining the overall success of the combined procedure.

e) DMEK combined with IOL implantation in aphakic eyes
Apart from the routine technique of phacoemulsification and in-the-bag IOL implantation, DMEK has also been combined with other methods of IOL implantation such as iris claw and scleral fixated IOLs in eyes with aphakic bullous keratopathy.\cite{140151} Seven consecutive eyes with bullous keratopathy, without adequate capsular support, underwent DMEK and posterior iris-claw implantation with favorable visual results and a mean endothelial cell loss of 24.8% at 7 months follow-up.\cite{151} Four eyes experienced graft dislocation which could be successfully reversed with air reinjection. Koçluk Y et al.\cite{150} combined the implantation of sutureless intrascleral fixation of IOL as well as sutured transscleral fixation with DMEK in 21 eyes with aphakic bullous keratopathy. Nine eyes required re-bubbling for settling detached grafts in the early postoperative periods. The overall graft adhesion rate was 85.7%, at last, follow-up visit.

f) DMEK in buphthalmic eyes with glaucoma drainage devices
Transplantation of normal or large diameter DMEK grafts has been seen to benefit buphthalmic eyes by transplanting a large number of endothelial cells with reduced risks of rejection in comparison to PK and DSAEK. The altered anatomy of the anterior segment poses several challenges in the form of difficult descemetorhexis due to the presence of Haab striae with string attached to the underlying stroma, presence of glaucoma drainage devices hindering in the unfolding of graft, and difficulty in achieving an adequate air fill of the anterior chamber interfering in proper graft adherence. The intraocular pressure should be adequately controlled before planning surgery in such eyes. Quilendrino R et al.\cite{152} observed graft detachment in two out of four adult eyes with buphthalmos, following DMEK. Mean endothelial cell loss ranged between 37 and 42%.

g) DMEK in eyes with prior failed graft
EK in eyes with prior failed PK allows visual rehabilitation with much less incidence of complications compared to a repeat full-thickness graft. Among the two popular techniques of EK, DMEK grafts are supposed to better fit the undersurface of a full-thickness graft. This is due to the flexibility of the graft which allows it to stretch across the irregular posterior surface of the graft, compared to a stiffer DSAEK graft. Clinical outcomes are limited by the optical quality of the prior graft and the presence of other ocular comorbidities\cite{153} and may not be comparable to that of a primary DMEK. These eyes are more prone to postoperative graft detachments and, therefore, should be closely monitored. In a study of 28 eyes with failed PK which underwent DMEK,\cite{155} 43% had graft failure and required repeat grafting. Factors such as better visual acuity at presentation, use of femtosecond laser for descemetorhexis, and a lower re-bubbling rate were associated with a lower risk of graft failure.

h) Outcomes of repeat DMEK
Deciding when to intervene secondarily, while observing eyes with detached grafts, is an important factor determining the outcomes of the second surgical procedure. Price et al.\cite{154} observed that in patients who received prompt intervention following a failed DMEK, the visual outcomes of secondary DMEK in such eyes were comparable with the primary DMEK. A paired fellow eye analysis was done in 29 eyes, wherein the outcomes of secondary DMEK were compared with the outcomes of primary DMEK performed in the fellow eye. The primary and secondarily grafted eyes were comparable in terms of visual acuity, central corneal thickness, and endothelial cell loss at 1-year follow-up. The authors advocated early intervention to minimize the duration of poor vision, symptomatic bullae, and restricted activities.

i) Femtosecond laser-assisted DMEK (F-DMEK)
The use of femtosecond laser for the creation of descemetorhexis in eyes undergoing DMEK is a newer addition to the armamentarium of laser refractive surgery. The creation of a precise and complete descemetorhexis in eyes undergoing DMEK is deemed important for the successful attachment of graft as any tags or residues remaining in the graft–host interface preclude the graft from adhering at that site. The use of femtosecond laser allows the creation of a precise descemetorhexis, avoiding inadvertent excess removal of host DM and limiting the size of the bare area. In a comparative study of 16 eyes with FECD, eyes that underwent F-DMEK had significantly less rate of postoperative graft detachment and consequently less number of re-bubblings required.\cite{155} Endothelial cell loss was significantly lower in the F-DMEK group till 2 years follow-up.

j) Outcomes of hemi-DMEK
Hemi-DMEK involves transplantation of “half-the-circle” of a full-sized untrephined DM. The concept of hemi-DMEK was devised as a potential method for increasing the pool of endothelial graft tissue.\cite{156} Instead of discarding the peripheral rim of endothelial cells, the full-size DM is cut into two semicircular halves and used for transplantation in two eyes. The preliminary outcomes of hemi-DMEK performed in 10 eyes with FECD suggested\cite{157} visual outcomes comparable with that of standard circular DMEK. The 6-month decline in ECD was, however, higher than the standard DMEK procedure. Of the 10 eyes, 4 had visually significant detachments, while another 4 had visually insignificant peripheral detachments. The authors suggested disparity in graft curvature and difference in the elastic properties of the central and peripheral cornea to account for difficult graft adhesion in these eyes. Long-term studies are warranted to fully understand the amount and pattern of endothelial cell loss and graft rejection rates, following hemi-DMEK.

The outcomes of DMEK in various clinical scenarios are summarized in Table 3.

Conclusion
The current review summarizes preoperative considerations, intraoperative nuances of different surgical techniques, and postoperative outcomes of DMEK. The review summarizes the advantages and disadvantages of different surgical modifications and enables us to customize surgical techniques keeping in mind the associated outcomes of each technique.

Financial support and sponsorship
Nil.
Conflicts of interest
There are no conflicts of interest.

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