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CYCLE XXXVIII

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Outcomes of Ultra-Thin Descemet Membrane Stripping Automated Endothelial Keratoplasty (UT-DSAEK) and Descemet Membrane Endothelial Keratoplasty (DMEK) for DSAEK decompensation

Scientific/Disciplinary Sector (SDS) MEDS-17/A

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SUMMARY

1. Abstract

Purpose:

Over the past decade, DSAEK has been among the most frequently performed endothelial keratoplasty procedures. As these grafts aged, an increasing proportion failed, eventually leading to a steadily growing demand for repeat transplantation. With the development of modern lamellar techniques, endothelial keratoplasty has become the surgery of choice for regrafting, with both UT-DSAEK and DMEK used to restore endothelial function.

According to the literature, graft survival after a previous transplant is substantially lower than in primary keratoplasty. In these patients, DMEK may be preferred because of its lower risk of endothelial immune rejection; however, previously operated eyes often exhibit poor anterior chamber visualization and complex anterior segment anatomy, increasing the technical complexity and fragility of the DMEK graft compared with UT-DSAEK. To date, robust evidence of the superiority of one approach over the other in eyes with failed DSAEK grafts is still lacking.

This study aimed to evaluate and compare the outcomes of DMEK and UT-DSAEK performed in eyes with failed DSAEK grafts, with particular attention to the impact of a prior immune-mediated endothelial rejection on postoperative outcomes and graft survival.

Methods

This ambispective, single-center interventional case series included 120 consecutive eyes undergoing repeated endothelial keratoplasty for DSAEK graft failure between January 2010 and December 2024. Sixty-six eyes received DMEK, and 54 underwent UT-DSAEK. Preoperative characteristics, perioperative data, and postoperative outcomes were collected at 1, 3, 6, 12, 24, 36, 48, and 60 months. Best-corrected visual acuity, endothelial cell density and loss, complication rate, rejection incidence, and graft failure were assessed.

Results

Both UT-DSAEK and DMEK led to a significant increase in BCVA 1 year after surgery (0.24 ± 0.22 and 0.26 ± 0.27 logMAR, respectively; $p<0.0001$), with no significant loss up to 5 years of follow-up. No significant difference between the two groups was found at any time point.

Mean donor ECD was comparable (UT-DSAEK 2507 ± 153 and DMEK 2539 ± 111 cells/mm²), but ECD significantly diverged from year 1 to year 4, showing greater cell loss in DMEK patients (UT-DSAEK 42.3% vs DMEK 53.3% at 1 year, $p = 0.002$), although

significance was lost by year 5, probably influenced by selective attrition of failing grafts. Cumulative graft survival for UT-DSAEK and DMEK was 94.3% and 86.3% at 1 year, and 52.2% and 54.7% at 5 years, respectively. Immune endothelial rejection occurred more frequently than typically reported for primary keratoplasty, but with similar rates between the two procedures. Notably, prior endothelial rejection did not worsen postoperative ECL in either group but was associated with significantly worse graft survival in the DMEK cohort.

Conclusions

In eyes undergoing repeat endothelial keratoplasty for failed DSAEK, both UT-DSAEK and DMEK provided comparable long-term visual outcomes and graft survival, despite a trend toward higher ECL in DMEK. The greater rejection rate and reduced graft survival compared with primary keratoplasty highlight the vulnerability of previously transplanted eyes, regardless of the retransplantation technique. Overall, these findings suggest that, after DSAEK failure, the outcomes of UT-DSAEK and DMEK are similar. Surgical choice should therefore be primarily guided by patients' characteristics and surgical preferences, rather than on the assumed superiority of either technique.

2. Introduction

2.1 Anatomy of the cornea

The cornea constitutes the anterior one-sixth of the outer layer of the eye. Its transparent, avascular structure serves both as a crucial barrier and a refractive component of the ocular system.

The cornea is one of the most densely innervated tissues in the human body, and its sensory nerve fibers are essential for maintaining epithelial integrity, reflex tearing, and the blink reflex.

Corneal sensory innervation is mediated by the long ciliary nerves originating from the ophthalmic branch of the trigeminal nerve. After entering the corneal stroma at the limbus, the fibers lose their myelin sheath and form stromal and sub-basal plexuses from which arise free nerve endings that penetrate the epithelium.

Thanks to the cornea's precisely organized microarchitecture, which provides transparency, light rays are transmitted and refracted to the retina with minimal scattering. The anterior corneal surface provides about +48.8 diopters (D). In contrast, the posterior surface has a compensatory −5.8 D effect, resulting in a total power of approximately +43 D, which makes up around two-thirds of the eye's total refractive power, establishing the cornea as its primary refractive element. The mean central corneal thickness (CCT) in healthy adults ranges from 520 to 550 µm, gradually increasing towards the periphery, where it may reach 650 to 700 µm.

Its structural and functional integrity depends on the close interplay among five distinct layers: the epithelium, Bowman's layer, stroma, Descemet membrane, and endothelium. [1,2]

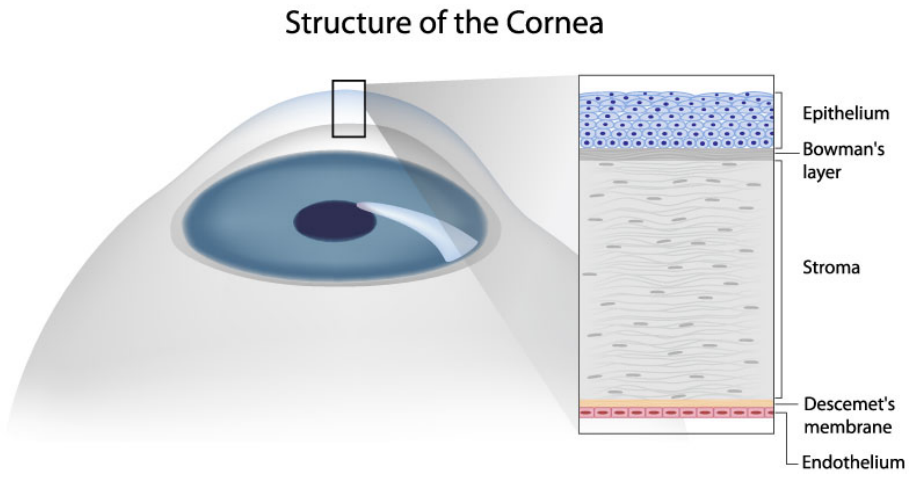


Figure 1 Schematic representation of the corneal layers [3]

Corneal Epithelium

The corneal epithelium makes up about 10% of the total corneal thickness, measuring roughly 50–55 µm at the center and gradually increasing toward the periphery. Along with the tear film, it constitutes the eye's first refractive surface and acts as the main barrier against environmental, chemical, and microbial threats.

It is composed of five to six layers of stratified, non-keratinized squamous epithelial cells. The cuboidal basal layer connects to the underlying Bowman's layer through hemidesmosomes, offering mechanical stability and shear resistance. Above this, several layers of polygonal wing cells and flattened superficial squamous cells are linked by tight junctions, forming a barrier that protects against external insults and prevents tear film fluid from penetrating the cornea.

Corneal epithelial cells have an average lifespan of 7 to 10 days, after which they undergo involution, apoptosis, and desquamation. Epithelial renewal is sustained by continuous centripetal migration of transiently amplifying stem cells that originate from the palisades of Vogt, a dedicated niche located in the corneoscleral limbus. This regenerative capacity enables epithelial homeostasis and rapid recovery following superficial epithelial injury.

The corneal surface is densely innervated by unmyelinated sensory fibers derived from the ophthalmic branch of the trigeminal nerve, which mediate corneal sensitivity and reflex tearing.

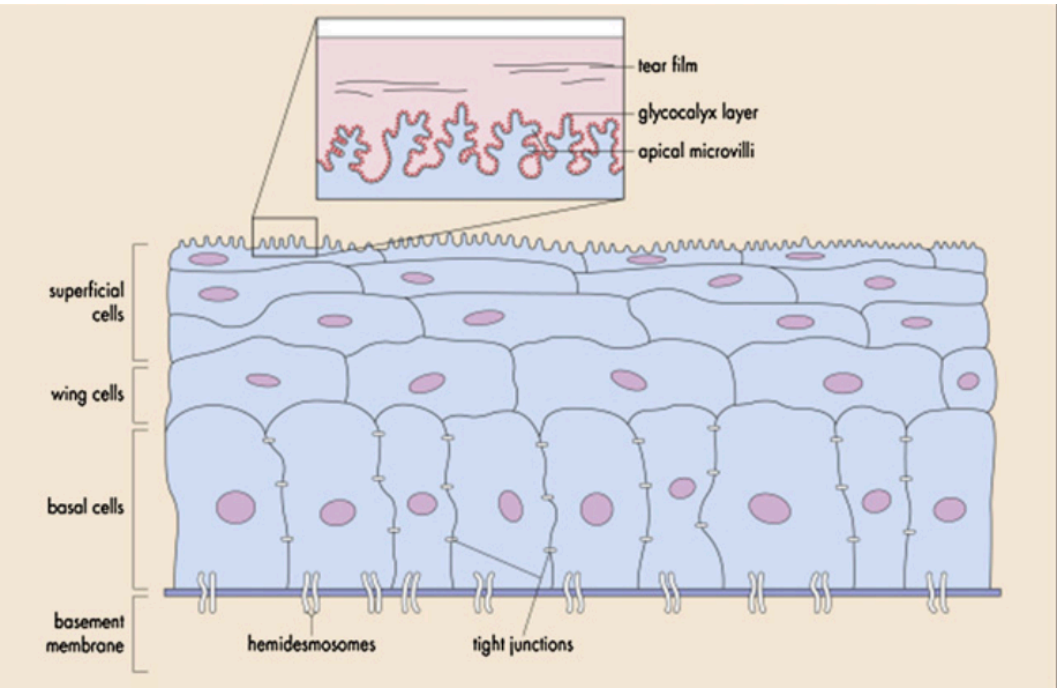


Figure 2 Cross-sectional representation of the corneal epithelial cell layers [4]

Bowman's Layer

Bowman's layer, situated between the epithelium's basal lamina and the anterior stroma, is an acellular, dense layer composed of type I and IV collagen fibers along with proteoglycans from the apical stroma. Its thickness ranges from about 8 to 12 micrometers, offering mechanical support and resistance against trauma and infection. Although its biomechanical role is limited, it remains clinically significant, especially in refractive surgery and anterior corneal diseases. Additionally, Bowman's membrane does not regenerate; once damaged, it is replaced by a fibrotic stromal scar tissue. [5]

Corneal Stroma

The stroma makes up about 90% of the corneal thickness and is key to maintaining the cornea's structural stability and transparency. This function is supported by its organized collagen lamellae, mainly composed of type I and V collagen, set within an extracellular matrix rich in proteoglycans like lumican, keratocan, and decorin. Proper spacing of collagen fibrils, maintained through interactions between stromal keratocytes and proteoglycans, minimizes light scattering and helps keep the tissue clear transparency. [6]

Keratocytes are the resident fibroblastic cells of the stroma that are essential for maintaining matrix balance and repair processes. Typically, they stay in a quiescent state under normal conditions but can become activated following injury or surgery, transforming into fibroblasts or myofibroblasts. This activation can lead to haze or scarring. Although the stroma lacks blood vessels, it receives nutrients and facilitates metabolic exchange through diffusion from the tear film at the front, the aqueous humor at the back, and the perilimbal capillary plexus peripherally. [2]

Descemet Membrane

The Descemet membrane (DM) is a specialized basement membrane produced by endothelial cells. Histologically, it appears with two distinct zones: an anterior banded layer formed during embryonic development and a posterior non-banded layer that is continuously deposited after birth by endothelial cells. As a result, the DM gradually becomes thicker over time, increasing from 3–4 μm in infancy to 10–12 μm in adulthood. It functions as the primary scaffold for endothelial adhesion; therefore, any damage or detachment of the DM can cause a loss of corneal transparency because of endothelial dysfunction and stromal swelling. [7]

Corneal Endothelium

The endothelium, which forms the innermost layer of the cornea, is only 4–6 μm thick but is crucial for maintaining corneal clarity and deturgescence through its barrier and pump functions. It consists of a single layer of hexagonal endothelial cells (ECs) facing the anterior chamber, with virtually absent proliferative capacity in vivo.

In infants, the normal endothelial cell density (ECD) usually ranges from 3000 to 3500 cells/mm². This density gradually decreases by about 0.6% annually in a normal cornea throughout adult life, along with increases in polymegethism pleomorphism. [8]

2.2 The key role of the corneal endothelium

Although only one cell thick, the endothelium is essential for keeping the cornea relatively dehydrated, a state called deturgescence. This condition ensures an optimal stromal hydration level of about 78%, which is vital for the health of the cornea transparency. [9]

To achieve this, the endothelium employs two complementary physiological mechanisms: a selective barrier that limits aqueous inflow into the stroma, and an active ion pump that expels excess fluid into the anterior chamber.

The interplay between these barrier and pump functions is explained by the “pump–leak” hypothesis, introduced by Maurice in 1957. This model describes how the endothelium permits a controlled leakage of fluid ("leak") from the aqueous humor into the stroma, which is then balanced by the active removal ("pump") of similar fluid amounts toward the anterior chamber. [10]

Barrier function

Endothelial cells form a semi-permeable layer due to the presence of various junctions, including tight junctions, adherens junctions, desmosomes, and gap junctions. These structures maintain cell communication and cohesion under normal intraocular pressure. These intricate junctional complexes are not fully occlusive, which limits paracellular fluid flow of aqueous humor and allows selective permeability for vital metabolites such as glucose, amino acids, and bicarbonate, essential for keratocytes and the epithelium.

Loss of barrier integrity, seen in conditions like Fuchs endothelial dystrophy or after surgical trauma, leads to increased stromal hydration and gradual visual decline caused by light scattering. [11]

Pump function

Complementing its barrier role, the corneal endothelium maintains stromal dehydration by actively transporting ions, thereby aiding the movement of water from the stroma to the anterior chamber. This process is mainly driven by the Na^+/K^+-ATPase enzyme, which is heavily expressed on the basolateral membranes of endothelial cells, alongside a network of Na+-bicarbonate cotransporters and ion exchangers. The orchestrated movement of ions and water produces a net outward flow of roughly 5–6 μL/cm²/hour, effectively offsetting stromal imbibition forces and preserving stable stromal water content under physiological conditions. [12]

2.3 Evaluation of the corneal endothelium

Various methods enable the clinical assessment of the corneal endothelium. Slit-lamp biomicroscopy, based on the principle of endothelial reflectivity, remains a simple yet informative tool in everyday practice. By positioning the slit beam at an oblique angle of about 30°–40° and making fine anteroposterior and lateral adjustments of the focal plane, it is possible to observe the endothelial reflex as a bright specular reflection originating from the posterior surface of the cornea. The image is best viewed with high magnification, typically 25× to 40×, and optimal illumination, which improves the visibility of the mosaic-like endothelial pattern. For quantitative analysis, specular microscopy is the preferred imaging method. This non-invasive technique uses specular reflection to visualize the endothelial cell layer in vivo, producing high-magnification images of the corneal endothelium that allow for the assessment of ECD (cells per mm²), size, and morphology.

It also visualizes endothelial guttae, which are areas of thickened Descemet's membrane appearing as dark, rounded holes within the endothelial mosaic. This feature is crucial for tracking endothelial cell counts in post-keratoplasty eyes or conditions such as Fuchs' dystrophy. Besides slit lamp and specular examinations, advanced imaging technologies can supplement endothelial assessment. In vivo confocal microscopy offers near-histological views of corneal layers, allowing direct observation of endothelial cells even when edema is present. Anterior segment optical coherence tomography (AS-OCT) provides cross-sectional images of the cornea, helping to measure thickness and identify subtle signs of edema or graft detachments. Combining these clinical and imaging techniques enables comprehensive evaluation of corneal endothelial health, supporting surgical planning and improving outcomes in corneal transplants patients. [13,14]

2.4 Diseases and dysfunction of the corneal endothelium

In Western countries, Fuchs endothelial corneal dystrophy (FECD) is the leading cause of visually significant endothelial loss and dysfunction, followed by post-traumatic or post-surgical cell loss, graft failure after transplants, and inflammatory conditions like herpetic endothelitis.

Human corneal endothelial cells are non-proliferative in vivo, as they are arrested in the G1 phase of the cell cycle. When endothelial cell loss happens, the remaining cells enlarge and spread to cover the area. According to literature, below a critical threshold of around 400–500 cells/mm², the remaining endothelium can no longer support corneal clarity, leading to endothelial decompensation, stromal and epithelial swelling, bullous keratopathy, and vision loss.

The endothelial cell density (ECD) alone does not fully indicate endothelial function. Other parameters, such as the variation in cell size and the percentage of hexagonal cells, also relate to functional performance. A coefficient of variation over 40% (normal is about 32%) and hexagonality below 50% (normal exceeds 60%) suggest a tissue that is quantitatively adequate but qualitatively compromised. This state increases the risk of corneal edema after eye surgery.

When endothelial failure becomes irreversible, replacing the endothelium surgically through keratoplasty remains the only effective and definitive treatment. [15,16]

2.4.1 Fuchs' Endothelial Corneal Dystrophy

Fuchs' Endothelial Corneal Dystrophy (FECD) is the leading indication for endothelial keratoplasty in Western countries. [17]

It is characterized by the formation of focal extracellular matrix excrescences on the Descemet membrane, known as guttae, and the degeneration of corneal endothelial cells, resulting from the interplay of various genes, lifestyle, and environmental factors.[18,19]

FECD typically exhibits a slowly progressing course, with individuals who may be asymptomatic or experience mild visual impairment in the early stages. As the disease progresses, the symptoms become more pronounced, often following a characteristic pattern ranging from morning hazy vision that gradually restores during the day to corneal decompensation, bullous keratopathy, and severe visual impairment.

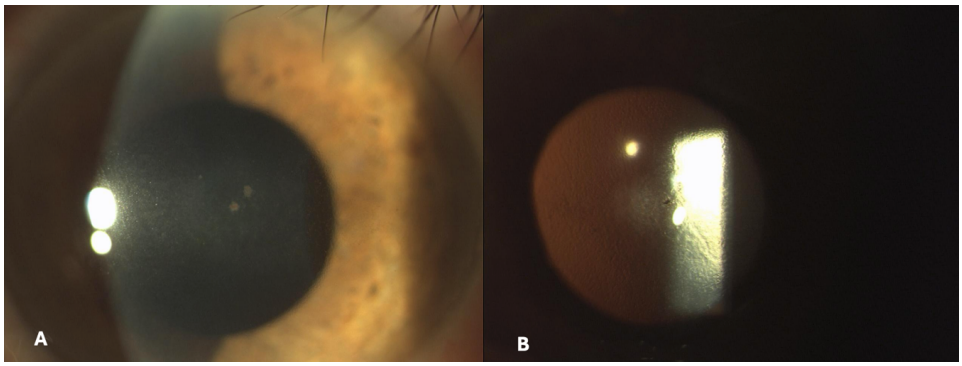


Figure 3 Figure A: slit-lamp picture of a cornea with mild edema and guttae; Figure B: guttae as seen at the slit lamp under high magnification and retroillumination

In the early stages of Fuchs' Endothelial Dystrophy, management is based on supportive measures such as hypertonic saline eye drops or ointments to help reduce corneal edema and alleviate symptoms. However, as corneal decompensation becomes irreversible, surgical intervention becomes necessary. [20]

2.4.2 Pseudophakic Bullous Keratopathy

Another major cause of bullous keratopathy is surgical trauma, with cataract surgery being the most common procedure involved. In these patients, Pseudophakic Bullous Keratopathy (PBK) is the preferred term. High ultrasound energy use and complex cases are significant factors contributing to cell loss after cataract surgery, which can lead to corneal decompensation even years later. The clinical course of PBK typically worsens over time, starting with patients experiencing blurred vision and progressing to severe vision loss as corneal edema and bullous keratopathy develop.

The diagnosis of PBK is confirmed through a comprehensive ophthalmic evaluation, beginning with a slit-lamp exam to identify epithelial defects or bullae, stromal scarring or edema, Descemet membrane folds, and endothelial decompensation. Additional diagnostic techniques such as specular microscopy, pachymetry, and AS-OCT can provide further insights into endothelial cell density, corneal thickness, and corneal opacities, respectively. Since symptoms vary, the best treatment for PBK can range from non-invasive methods like hypertonic saline eye drops and bandage contact lenses for milder cases to surgical removal of the damaged endothelium with a keratoplasty for more severe cases stages. [21]

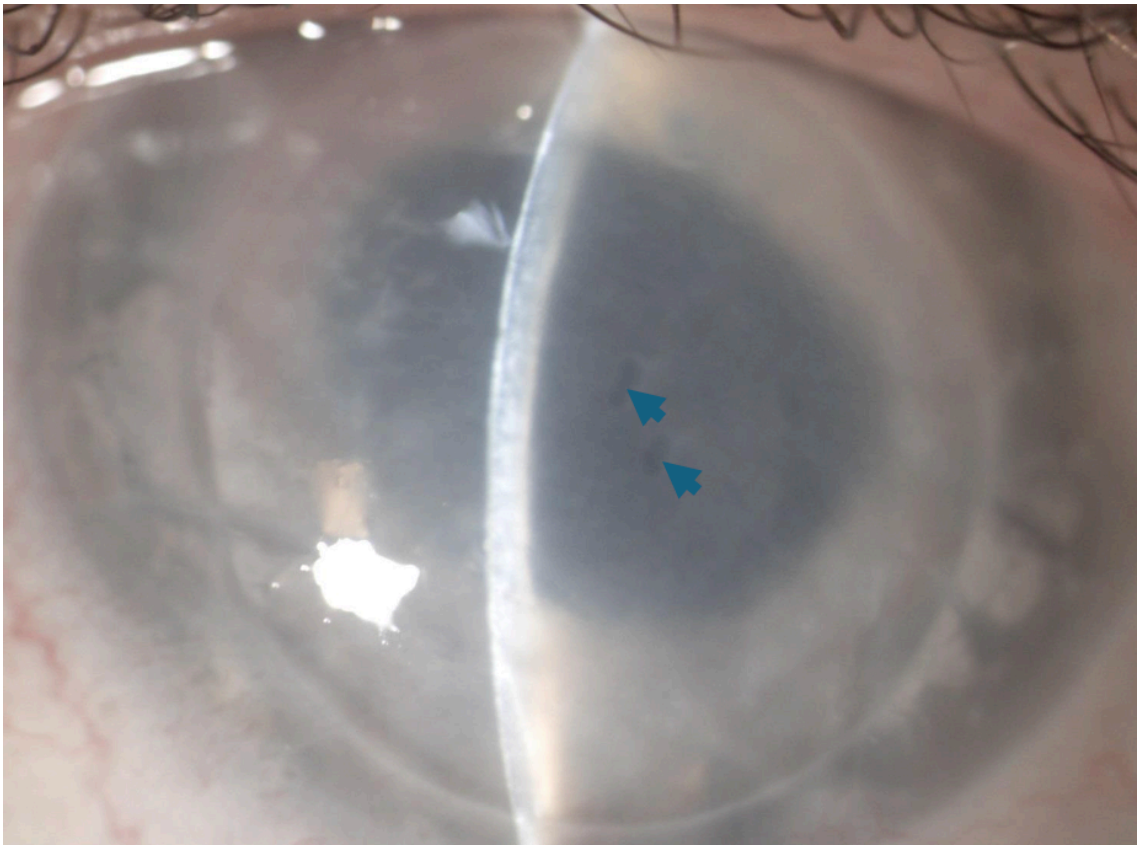


Figure 4 Slit-lamp photograph of an eye with pseudophakic bullous keratopathy, showing corneal edema and epithelial bullae (blue arrowheads)

2.4.3 Herpetic Endothelitis

Endothelitis is characterized by inflammation of the corneal endothelium caused by various factors. Its typical signs include corneal edema along with keratic precipitates (KP) and, in cases of anterior uveitis, inflammation of the anterior chamber. Common symptoms include vision problems, eye pain, and photophobia.

Among the potential causes of endothelitis, Herpes Simplex Virus (HSV) is significant due to its high prevalence in the population. HSV is transmitted through direct contact with mucous membranes.

The initial acute episode is usually mild or subclinical, resembling typical viral conjunctivitis. After remission, the virus remains dormant in the ophthalmic division of the trigeminal ganglion. During a relapse, the virus may reactivate and involve any layer of the cornea. Epithelial keratitis is usually characterized by a dendritic or geographic ulcer that stains positively with fluorescein.

Stromal keratitis is mediated by a type III immune reaction leading to stromal opacities with a surrounding ring of deposited immunocomplexes, known as the Wessely ring.

Endothelitis, mediated by a type IV immune reaction, manifests with disciform KP, corneal edema, and can be associated to anterior chamber inflammation, which can eventually lead to elevated intraocular pressure in case of trabecular meshwork involvement. [22]

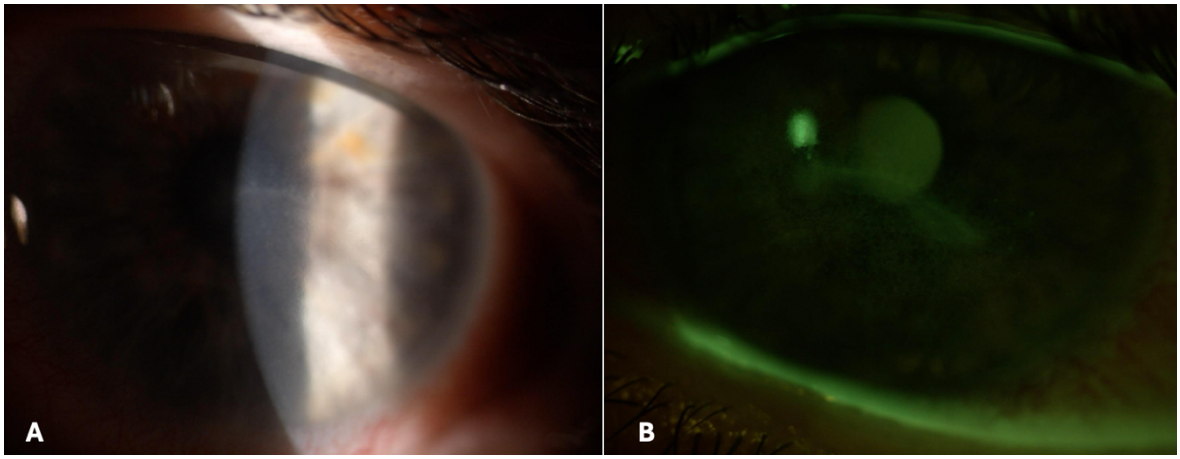


Figure 5 Slit-lamp photograph of an eye with herpetic endothelitis. Figure A shows the epithelial defect and corneal edema with fine, whitish KP on the endothelium. Figure B shows the epithelial dendritic ulcer stained with fluorescein

Although slit-lamp examination remains the primary diagnostic method, laboratory testing, such as polymerase chain reaction (PCR) identification of HSV-DNA on corneal swabs or aqueous samples, has proven a valuable adjunct in equivocal cases. [23]

Herpetic endothelitis management involves a combination of antiviral and anti-inflammatory treatments, given both topically and systemically with a gradual tapering approach. However, in cases of irreversible endothelium damage, keratoplasty remains the only option. [24]

2.5 Evolution of keratoplasty techniques for endothelial decompensation

Over the past 20 years, the field of keratoplasty has seen significant technological advancements and shifts in trends. Early in the century, penetrating keratoplasty (PK) was the preferred procedure for treating corneal diseases, involving the replacement of all layers of the host cornea with a full-thickness donor graft.

Recently, the development of selective lamellar keratoplasty techniques has enabled the replacement of only the affected corneal layers, offering significant benefits over the earlier method.

The following paragraphs provide an overview of the most commonly used techniques for treating endothelial-decompensated corneas (Fig. 5).

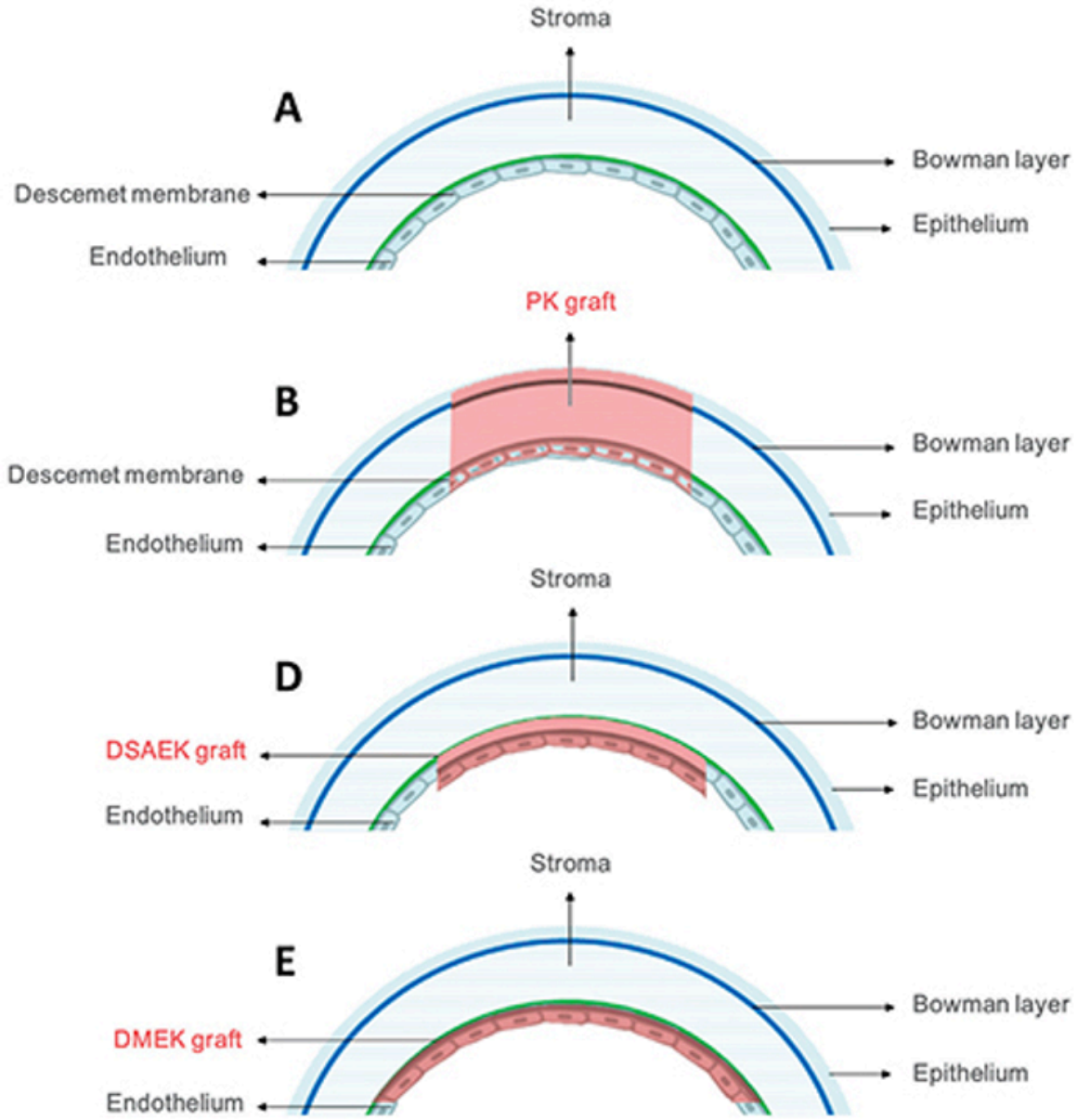


Figure 6 Schematic representation of the most commonly used keratoplasty techniques for treating decompensated corneas.
PK = penetrating keratoplasty; DSAEK = Descemet Stripping Automated Endothelial Keratoplasty; DMEK = Descemet Stripping Endothelial Keratoplasty

2.5.1 Penetrating keratoplasty

The first successful attempt at human corneal transplantation dates back to 1905, when Dr Eduard Zirm implanted a full-thickness 5 mm corneal graft in the eye of a 45-year-old man suffering from severe alkali-mediated corneal burn. [25]

Since then, PK has received only minor technical improvements and remained the preferred technique until the early 21st century and is still an essential surgical option in cases where all corneal layers are compromised.

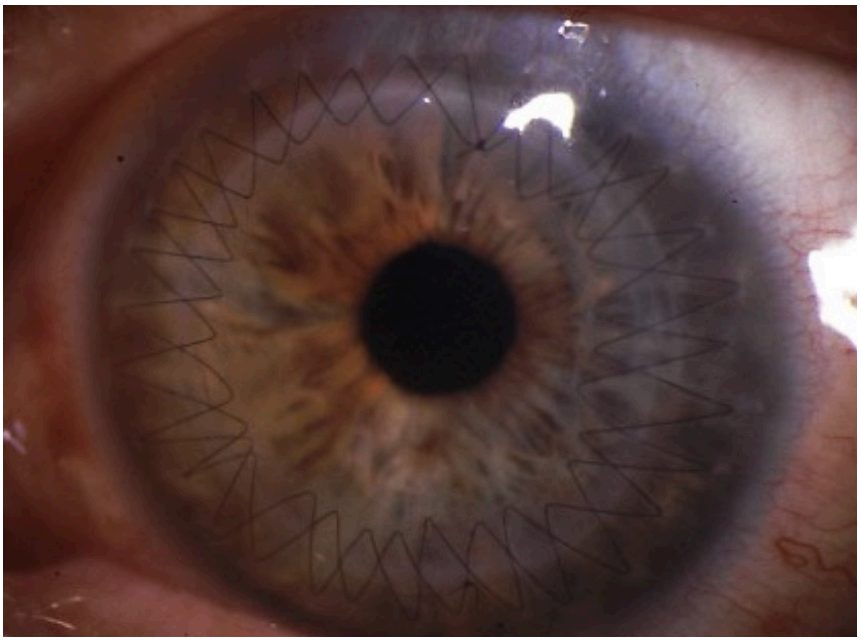


Figure 7 Slit-lamp photograph of an eye following penetrating keratoplasty. A double 16-bite continuous 10-0 Nylon suture is visible along the graft-host interface

Despite its conceptual simplicity, which involves placing a "perfect disc in a perfectly round hole" and restoring corneal transparency, regardless of which layer is compromised, PK is associated with several limitations.

Wound healing is a slow process, requiring one year or more for complete suture removal and full wound stabilization. During this prolonged period, visual acuity can be limited by severe corneal distortion and high irregular astigmatism, which could persist even after stitch removal.

Furthermore, using a full-thickness allograft to exchange all corneal layers, if not necessary, exposes the patient to an unnecessarily higher risk of immunological rejection. [26,27]

2.5.2 Posterior Lamellar Keratoplasty (PLK), Descemet Stripping endothelial Keratoplasty (DSEK), Descemet Stripping Automated Endothelial Keratoplasty (DSAEK), and Ultra-Thin Descemet Stripping Automated Endothelial Keratoplasty (UT-DSAEK)

Compared to PK, endothelium keratoplasty (EK) replaces only the diseased endothelium with healthy tissue.

In 1998, Melles and his team described a technique for placing a graft consisting of endothelium, Descemet's membrane, and a layer of posterior stroma into a pocket dissected in the back of the host cornea, a procedure called posterior lamellar keratoplasty (PLK). [28]

A few years later, the same team realized that donor tissue could adhere to the host stroma solely by surface tension and a high-pressure air bubble in the anterior chamber after stripping Descemet's membrane. This led to the invention and description of Descemet stripping endothelial keratoplasty (DSEK). [29]

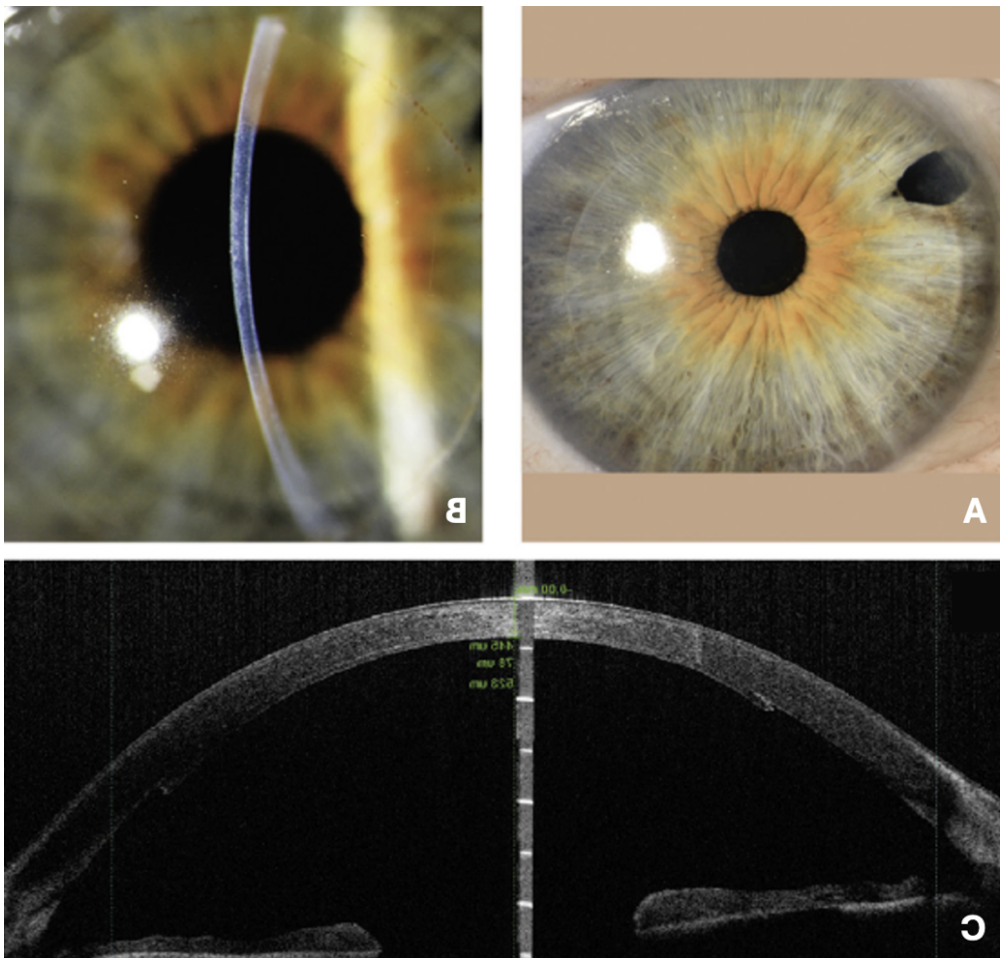


Figure 8 Clinical and Tomographical appearance of DSAEK. A) slit-lamp photograph of an eye following DSAEK; B) high-magnification highlight of the graft-host interface; C) AS-OCT image of the DSAEK lenticule, with good apposition and centering to the posterior stroma. Noted in green is the 178 µm thickness of the lamella

One of the main challenges with lamellar keratoplasty was manually preparing and cutting the donor cornea. This issue was addressed in 2004 when surgeons started using the microkeratome to cut the posterior lamella of the graft, a variation of the procedure known as Descemet stripping automated endothelial keratoplasty (DSAEK).

In 2009, Busin and his team ultimately perfected this technique by standardizing a procedure to obtain and deliver donor lamellae thinner than 100 µm, therefore called Ultra-Thin DSAEK (UT-DSAEK). [30]

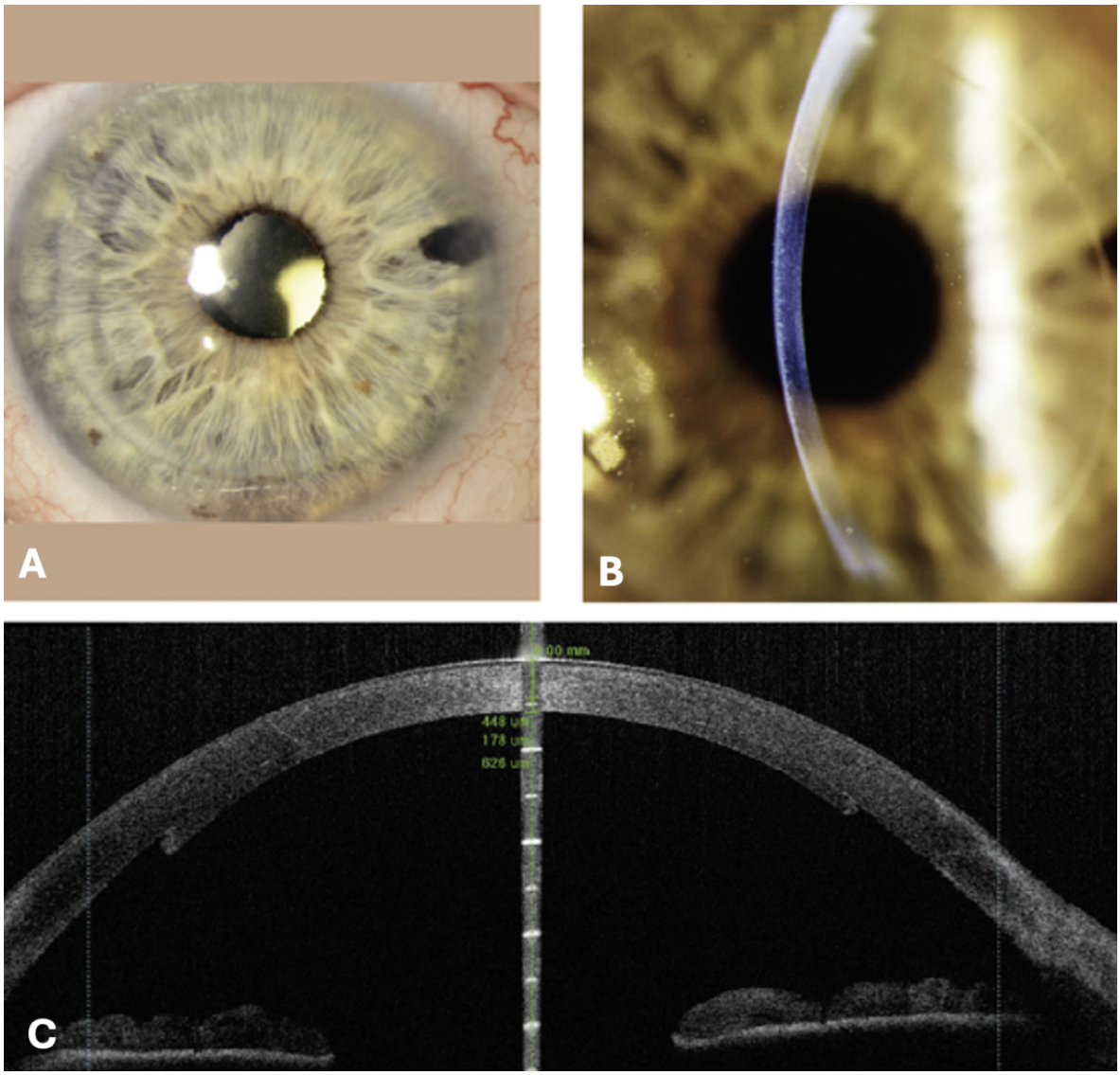


Figure 9 Clinical and Tomographical appearance of UT-DSAEK. A) slit-lamp photograph of an eye following UT-DSAEK; B) high-magnification highlight of the graft-host interface; C) AS-OCT image of the DSAEK lenticule, with good apposition and centering to the posterior stroma. Noted in green is the 78 µm thickness of the lamella

Following its introduction, endothelial keratoplasty has rapidly become the procedure of choice for patients with diseased endothelia and healthy stromas, thanks to numerous advantages compared to PK.

Being a closed globe surgery, EK provides a significantly lower risk of sight-threatening complications such as expulsive hemorrhages. endophthalmitis, and with no associated lifetime risk of globe rupture due to wound dehiscence. [31]

Furthermore, visual recovery following DSAEK and UT-DSAEK is significantly faster than PK, with a main incision of just 3 mm and fewer sutures that can be removed as early as 2 months postop, resulting in a minor, rarely irregular degree of astigmatism. [32]

Moreover, EK offers a lower risk of immune rejection because a smaller amount of tissue is transplanted, thereby reducing the alloantigens. [33]

The complexity of this technique primarily resides in the preparation and delivery of the graft within the anterior chamber.

Nowadays, however, many surgeons can obtain a pre-cut donor cornea from eye banks, thus eliminating the need to prepare the tissue intraoperatively.

In case of graft mispositioning, detachment, or graft dislocation, repositioning and rebubbling can be attempted both intraoperatively and postoperatively.

2.5.3 Descemet Stripping Endothelial Keratoplasty (DMEK)

In 2006, Melles introduced a new type of EK, where the donor tissue included only the DM and the overlying endothelium, a procedure known as Descemet membrane endothelial keratoplasty (DMEK). [34]

Compared to DSAEK, the absence of donor stroma allows for a thinner graft, approximately 20μm thick, which reduces the risk of immune rejection and provides a smoother graft-host interface, resulting in faster visual recovery and, in some cases, improved visual outcomes. On the other hand, handling DMEK is significantly more challenging, resulting in a higher risk of overmanipulation, endothelial damage, primary graft failure, and graft detachment compared to DSAEK techniques. [35–37]

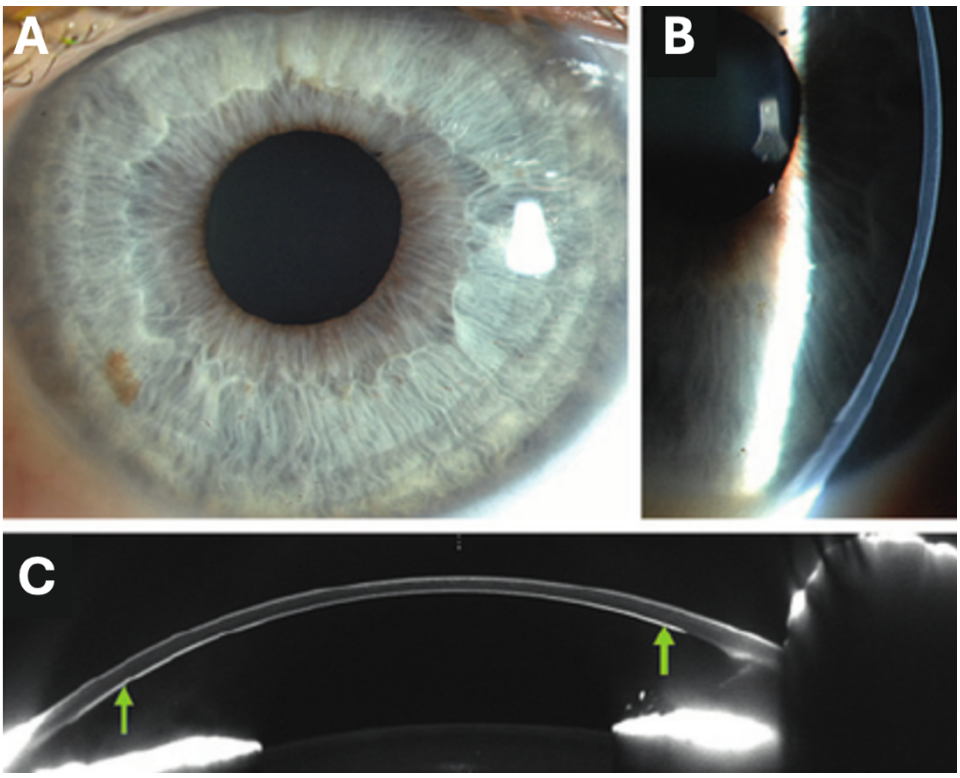


Figure 10 Clinical and Tomographical appearance of DMEK. A) slit-lamp photograph of an eye following DMEK; B) high-magnification highlight of the graft-host interface; C) AS-OCT image of the DMEK lenticule (indicated by the green arrows), with good apposition and centering to the posterior stroma.

2.5.4 Current Trends in Keratoplasty

Overall, keratoplasty is currently the most commonly performed transplant worldwide. Since the beginning of this century, the number of keratoplasty procedures has steadily increased, and trends in the types of keratoplasty have experienced significant changes, as shown in data provided by Eye Banks worldwide.

According to the Eye Bank Association of America's (EBAA) 2012 report, 2012 marked the year when the number of EKs surpassed the number of PKs, making it the most frequently performed keratoplasty technique, a trend that continues to this date. [38]

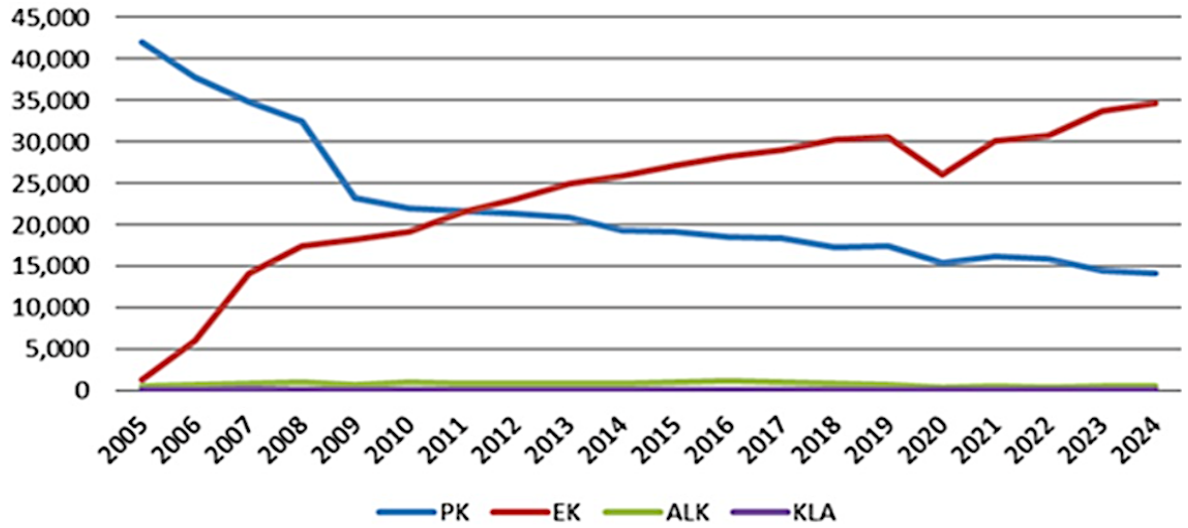


Figure 11 Total number of keratoplasty procedures performed in the US each year from 2005 to 2024, reported by the EBAA.
PK = Penetrating Keratoplasty; EK = Endothelial Keratoplasty (DSAEK + DMEK); ALK = Anterior Lamellar Keratoplasty; KLA = Keratolimbal Allograft [38]

When analyzing the number of EK procedures performed each year in detail, it can be seen that DMEK has progressively gained popularity over DSAEK, eventually becoming the most commonly performed keratoplasty technique in 2023. This trend reflects the increasing surgical expertise and familiarity with DMEK over time, as surgeons gradually overcame initial technical challenges and gained more experience.

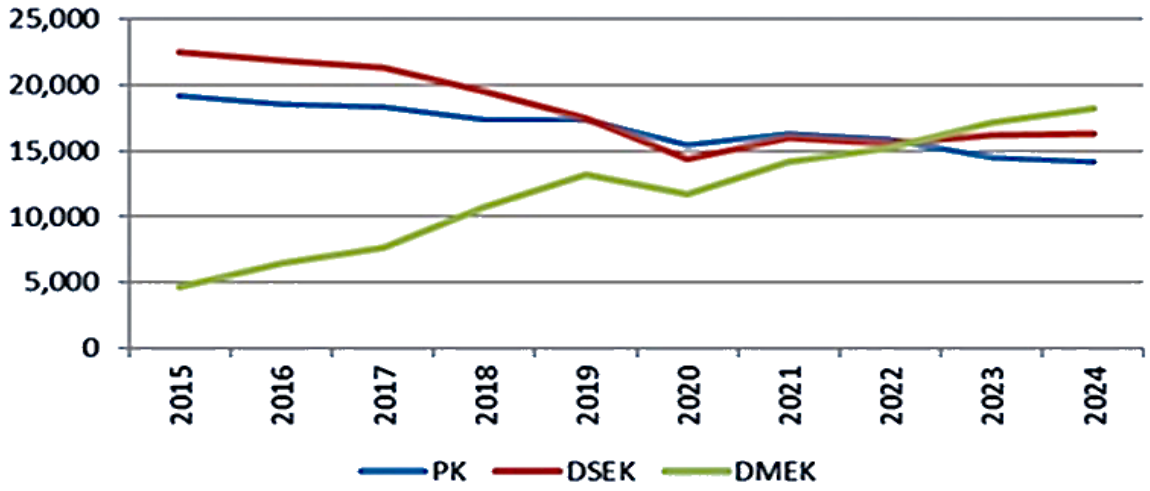


Figure 12 Total number of procedures performed in the US each year from 2015 to 2024, reported by the EBAA. [38]
PK = Penetrating Keratoplasty; DSEK = Descemet Stripping Endothelial Keratoplasty; DMEK = Descemet Membrane Endothelial Keratoplasty

In parallel, in the last 20 years, the leading indication for keratoplasty shifted markedly from stromal or full-thickness disease to endothelial cell failure, further contributing to the increasing popularity of the newly developed EK techniques.

Overall, an estimated 180'000 corneal transplants are performed globally each year. [39]

Although survival outcomes vary among keratoplasty types and patient-related characteristics, the cumulative long-term graft survival rate is typically reported to be in the range of 70%–90%, with EKs showing a higher survival rate compared to PK. [40–43]

Considering that all these studies describe patients who underwent surgery many decades ago, this explains the recent increase in regrafting cases, making failed grafts the second most common cause of keratoplasty in recent years, after FECD, which remains the consistently leading indication for corneal transplantation. [38]

2.6 Graft Failure

A corneal graft failure is defined as any graft that irreversibly loses its clarity, resulting in a decrease in vision that requires repeat transplantation, regardless of tissue attachment status. The following paragraphs describe the most common method for classifying graft failure.

2.6.1 Early or Primary Graft Failure (PGF)

As described in the Cornea Preservation Time Study, early or primary graft failure (PGF) refers to a cornea that fails to clear within 8 weeks postop. [44]

Common causes include deficiencies in the donor tissue, incorrect preservation, or improper surgical manipulation during the procedure. This is confirmed by the literature, which reports a higher incidence of PGF in EK procedures compared to PK, and in particular for DMEK compared to DSAEK. [45]

2.6.2 Late or Secondary Graft Failure (SGF)

Late or secondary graft failure (SGF) occurs in a previously functional graft that loses clarity over time. This can happen due to non-immunological causes, such as surface failure in limbal stem cell deficiency, infection, glaucoma, trauma, or mere cell loss over time.

As with any allograft, though, the donor cornea is also subjected to the risk of eliciting an endothelial immune rejection mediated by the host's immune system, described in more detail in the following paragraph.

2.6.3 Endothelial Immune Graft Rejection

Despite the cornea's relative immune and angiogenic privileges, the most common cause of corneal graft failure is allogenic rejection. [46]

Thus far, several risk factors have been identified, including younger or diabetic recipients, active host inflammation or neovascularization, previous history of herpetic eye diseases, glaucoma, repeated grafts, and concurrent surgeries. At the same time, HLA Class II matching did not reduce the risk of allograft rejection, and ABO blood type compatibility provided incongruent evidence. [47,48]

Lamellar keratoplasty, whether anterior or posterior, exhibits a lower rejection risk compared to PK, likely due to a smaller antigen load resulting from transplanting less tissue. It also avoids endothelial rejection in DALK cases and benefits from anterior chamber-associated immune deviation, as well as the absence of stromal sutures in endothelial keratoplasty. [46,49]

Consistent with these theories, several reports have shown that DMEK has a significantly lower risk of rejection compared to DSAEK and UT-DSAEK and is therefore increasingly performed in eyes with a “high-risk” of rejection. [42,43,50]

Common clinical manifestations of graft rejection include corneal edema, vascularization, and KP. Immunologically damaged endothelium is typically separated by healthy endothelium by a line of mononuclear cells, called the Khodadoust line, which expands gradually with time as the damage progresses over the donor tissue.

Currently, corticosteroids, both topical and systemic, are the mainstay of prophylaxis and treatment of rejection. If the signs of rejection do not recede and/or the cornea does not clear within 2 months of treatment, the diagnosis of immunologic graft failure is made.

2.7 Purpose of the Study

In the past decade, DSAEK has been one of the most performed keratoplasties each year. Nowadays, a constantly increasing number of those grafts are progressing to failure and require re-transplantation. Since the advent of modern lamellar keratoplasty, EK has been the preferred surgical option for failed grafts, with DSAEK as well as DMEK utilized to restore endothelial function.

As demonstrated by multiple reports, long-term cumulative graft survival is significantly lower for eyes with a previous failed graft than for other keratoplasty indications. [51]

DMEK may be preferred for these eyes due to its lower risk of endothelial immune rejection; however, previously operated eyes often have poor anterior chamber visualization and complex anterior segment anatomy, making graft manipulation in DMEK

more challenging and potentially damaging than in DSAEK. Currently, evidence of the superiority of one technique over the other in this subset of patients is still lacking.

This study aims to compare the outcomes of DMEK and DSAEK in eyes with failed DSAEK grafts with a follow-up up to 5 years, focusing on differences between eyes with and without an immunological rejection history.

3. Materials and Methods

This was a single-center, retrospective, and prospective interventional case series, including eyes that underwent repeated endothelial keratoplasty for DSAEK graft failure between January 2010 and December 2024 at a tertiary-level center (Ospedali Privati Forlì, Forlì, Italy).

The study adhered to the tenets of the 2013 Declaration of Helsinki and was approved by the local Institutional Ethics Committee, Comitato Etico Ospedali Privati Forlì in Forlì, Italy. All patients involved signed an informed consent form before surgery or data collection, as applicable.

A total of 120 consecutive eyes were included, of which 66 underwent DMEK and 54 underwent repeated DSAEK (re-DSAEK). Patients from each group were then assigned to subgroups according to their previous history of immunological endothelial rejection.

Surgical Procedure and Postoperative Management

Both surgical procedures were performed according to previously described and standardized techniques. [30,52]

In reDSAEK patients, donor tissue was prepared intraoperatively. The donor cornea was mounted on an ALTK artificial anterior chamber (Moria, Antony, France), and central corneal thickness was measured using ultrasound pachymetry, and a lamella of anterior stroma was cut with a microkeratome. The choice of the microkeratome head was calculated to obtain a graft thinner than 130 µm. In DMEK patients, the tissue was provided pre-cut, pre-marked and pre-stripped from the eye bank.

In the host cornea, a caliper was used to measure the diameter of the cornea and determine the appropriate graft size and the relative trephine. A main 3mm temporal corneoscleral incision or scleral tunnel was created for DSAEK and DMEK patients, respectively.

A 25-gauge needle was used to detach the failed DSAEK graft from the posterior corneal surface under continuous irrigation with balanced salt solution (BSS). If not already present, an inferior iridectomy is performed to prevent postoperative pupillary block.

For DSAEK, the donor lamella was then charged on a dedicated glide (Busin glide), properly oriented with the endothelium facing downwards, and slid into the anterior chamber through the temporal incision with a pull-through movement. The glide was then removed, and the DSEAK-graft was carefully unfolded and centered in the host's anterior chamber.

For DMEK, the donor graft is tri-folded with endothelium-in and then transferred via a sterile therapeutic soft contact lens (Sooft, Montegiorgio, Italy) into a BSS-filled IOL cartridge (MDJ Company, La-Monniere-le-montel, France). The DMEK graft was then delivered bimanually under continuous BSS irrigation with an anterior chamber maintainer (Moria SA, Antony, France) from the 12 o'clock position.

In both procedures, after the correct positioning of the donor lamella, a high-pressure air bubble was injected inside the anterior chamber underneath the graft to promote adhesion to the posterior stroma of the host cornea.

At the end of the procedure, after suturing tightly the incisions and hydrosuturing the paracentesis, a solution of triamcinolone acetonide and gentamicin sulfate 0.3% was injected subconjunctivally.

Every patient was seen as early as 2 hours after surgery to remove some of the air in the anterior chamber, if necessary.

At discharge, a fixed combination of betamethasone 0.2% and cloramphenicol 0.5% (Thèa Farma S.p.A., Milan, Italy) ophthalmic solution was started every 2 hours daily and tapered off to 4 times daily over the first postoperative month. Subsequently, topical antibiotic treatment was discontinued, while betamethasone was replaced with fluorometholone, which was slowly tapered to once daily and administered indefinitely.

Steroid-induced ocular hypertension was treated with intraocular pressure-lowering agents as needed. Stitches, when present, were removed 3 months after surgery.

Data collection

The collected data were recorded in an electronic database using Microsoft Excel (Microsoft Corp., Redmond, Washington, USA).

The best corrected visual acuity (BCVA), lens status, indication for initial transplantation, and etiology of DSAEK failure were evaluated as preoperative characteristics for each patient. Intraoperatively, the number of triple procedures and the donor endothelial cell density (ECD), as indicated by the eye bank providing the tissue, were documented.

Postoperatively, the occurrence of rebubbling, rejection, and graft failure was recorded.

Follow-up examinations were conducted at intervals of 1, 3, and 6 months, as well as at 1, 2, 3, and 5 years. At each visit, BCVA, ECD, and endothelial cell loss (ECL) were measured.

BCVA was assessed using Snellen charts, and the value was later converted to the logarithm of the minimum angle of resolution (logMAR) for descriptive and analytical purposes.

Preoperative ECD was obtained from the graft report provided by the eye bank supplying the tissues. Postoperative ECD was measured using the EM-3000 non-contact specular microscope (Tomey Corporation, Tokyo, Japan) and expressed as cells per mm^2. ECL was calculated by subtracting each ECD from the previous one and expressed as a percentage of the initial donor ECD.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 10 (GraphPad Software, LLC, Boston, Massachusetts, USA).

The Shapiro-Wilk test was used to assess normality in continuous variables. Comparisons between the two groups were performed using the Mann-Whitney U test for normally distributed variables, and the independent-samples T-test for normally distributed variables.

Comparison between preoperative and postoperative measures was performed using the paired t-test for parametric variables and the Wilcoxon signed-rank test for non-parametric variables.

Categorical variables were expressed as percentages and compared using Fisher's exact test or the χ^2 test, as appropriate.

Graft survival was expressed as a percentage using cumulative probability curves generated by Kaplan-Meier analysis and compared with the log-rank test.

Lastly, subgroup analysis was performed in order to evaluate the influence of a previous history of immune rejection on endothelial cell loss and graft survival.

4. Results

A total of 120 eyes of 120 patients with failed DSAEK were recruited for this study.

Of these, 54 eyes underwent UT-DSAEK (45.0%), while 66 (55.0%) eyes underwent DMEK.

	UT-DSAEK (n=54)	DMEK (n=66)	p-value
Age (years)	67.4 ± 14.4	72.2 ± 13.5	**0.0267**
Male	20 (37%)	28 (42.4%)	0.58
Phakic	5 (9.3%)	10 (15.2)	0.41
Indication for previous DSAEK:			
• **Fuchs**	27 (50%)	40 (60.6%)	0.56
• **PBK**	21 (38.9%)	21 (31.8%)	0.37
• **HSV**	5 (9.3)	4 (6.1%)	0.74
• **Trauma**	1 (1.9%)	1 (1,5%)	0.99
Previous history of rejection	11 (20.4%)	13 (19.7%)	0.99
Time from 1st to 2nd to graft (months)	25.79 ± 30.99	75.55 ± 38.96	**< 0.001**
BCVA (logMAR)	0.92 ± 0.34	0.90 ± 0.35	0.43

Table 1 Baseline characteristics

Table 1 describes the demographic and clinical characteristics of the population at baseline.

The UT-DSAEK group was significantly younger than the DMEK group (67.4 ± 14.4 vs. 72.2 ± 13.5 years, $p < 0.05$) and underwent repeated endothelial keratoplasty significantly sooner (25.79 ± 30.99 vs. 75.55 ± 38.96 years, $p < 0.001$).

No statistically significant difference was observed in the percentage of males and in the number of phakic patients.

The two groups were also statistically similar in the distribution of indications for the previous DSAEK graft, and no significant difference was observed in the number of patients who experienced immune endothelial rejection.

In particular, for both groups in our cohort, the leading indication for the first transplant was FECD (50% vs 60.6%, $p = 0.56$), followed by PBK (38.9% vs 31.8%, $p = 0.37$), HSV (9.3% vs 6.1%, $p = 0.74$), and trauma (1.9% vs 1.5%, $p = 0.99$).

Preoperative BCVA was also comparable, with a mean value of 0.92 ± 0.34 logMAR and 0.90 ± 0.35 logMAR (p=0.43) in the UT-DSAEK and DMEK groups, respectively.

	UT-DSAEK (n=54)	DMEK (n=66)	p-value
Triple Procedure	3 (5,6%)	2 (3%)	0.66
Rebubbling	6 (11.1%)	8 (12.1%)	0.99
Cystoid Macular Edema	6 (11.1%)	12 (18.2%)	0.32
New rejection episode:	9 (16.6%)	10 (15.2%)	0.99
• **With history of rejection**	0 (0.0%)	3 (4.5%)	0.21
• **Without history of rejection**	9 (16.6%)	7 (10.6%)	0.21

Table 2 Distribution of triple procedures and key postoperative complications in the UT-DSAEK and DMEK groups

The average follow-up time did not differ between the UT-DSAEK and DMEK patients (38.31 ± 20.33 vs. 33.94 ± 18.92, p = 0.26).

No intraoperative complications were recorded, and a similar number of triple procedures were performed in both groups. No statistically significant difference was observed in the occurrence of cystoid macular edema or in the rate of rebubblings performed.

The number of new immune endothelial rejection episodes was comparable in UT-DSAEK and DMEK patients (p = 0.99). Furthermore, patients with a history of previous immune endothelial rejection showed no difference compared to patients who had not already experienced rejection in the previous graft, either in the UT-DSAEK group (0.0% vs. 16.6%, p = 0.18) or the DMEK group (4.5% vs. 10.6%, p = 0.40).

Best Corrected Visual Acuity Comparison

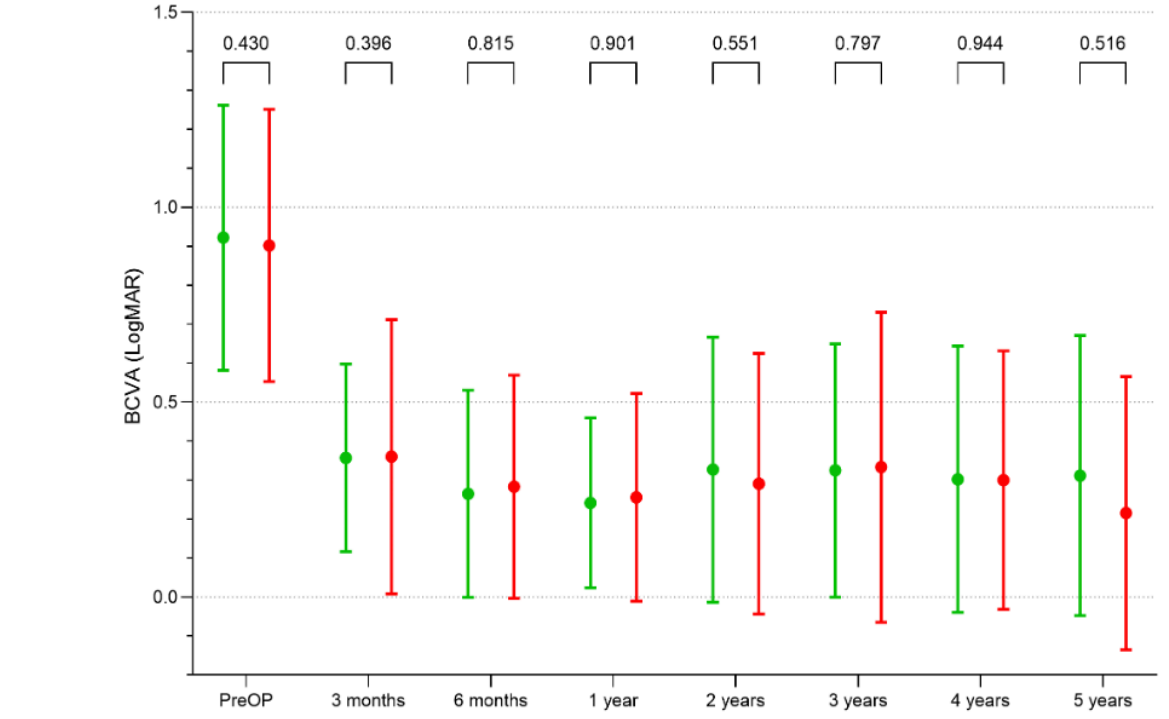
Figure 13 illustrates the mean BCVA values for each group across all follow-up visits.

Patients undergoing UT-DSAEK and DMEK exhibited a comparable preoperative BCVA (0.92 ± 0.34 vs 0.90 ± 0.35 logMAR, p = 0.43). After surgery, BCVA improved significantly in both groups.

In the UT-DSAEK cohort, BCVA increased to 0.24 ± 0.22 logMAR at 1 year ($p < 0.0001$), with no significant loss up to 5 years ($p = 0.16$).

Similarly, in the DMEK group, BCVA improved to 0.26 ± 0.27 logMAR after 1 year ($p < 0.0001$), with no significant decline at the last follow-up visit ($p = 0.48$).

Overall, no statistically significant difference was found between UT-DSAEK and DMEK across the 5-years follow-up.



	PreOP	3 months	6 months	1 year	2 years	3 years	4 years	5 years
UT-DSAEK	0.92 ± 0.34 (n=54)	0.36 ± 0.24 (n=50)	0,27 ± 0,27 (n=50)	0,24 ± 0,22 (n=46)	0,33 ± 0,34 (n=41)	0,33 ± 0,33 (n=34)	0,30 ± 0,34 (n=26)	0,31 ± 0,36 (n=22)
DMEK	0.90 ± 0.35 (n=66)	0.36 ± 0.35 (n=55)	0,28 ± 0,29 (n=53)	0,26 ± 0,27 (n=50)	0,29 ± 0,33 (n=44)	0,33 ± 0,40 (n=36)	0,30 ± 0,33 (n=21)	0,22 ± 0,35 (n=13)

Figure 13 Comparison of best corrected visual acuity (BCVA) measured in logMAR and expressed as mean ± standard deviation

	3 Months			6 Months			12 Months			24 Months			36 Months			48 Months			60 Months		
	≥ 20/40	≥ 20/25	≥ 20/20	≥ 20/40	≥ 20/25	≥ 20/20	≥ 20/40	≥ 20/25	≥ 20/20	≥ 20/40	≥ 20/25	≥ 20/20	≥ 20/40	≥ 20/25	≥ 20/20	≥ 20/40	≥ 20/25	≥ 20/20	≥ 20/40	≥ 20/25	≥ 20/20
UT-DSAEK	60.0%	12.0%	8.0%	70.0%	42.0%	14.0%	65.2%	50.0%	21.7%	68.3%	39.0%	12.2%	61.8%	41.2%	20.6%	65.4%	46.2%	30.8%	59.1%	54.5%	31.8%
DMEK	61.3%	31.5%	7.4%	61.5%	40.4%	19.2%	66.0%	40.0%	24.0%	70.5%	40.9%	25.0%	62.9%	42.9%	25.7%	61.9%	42.9%	28.6%	84.6%	53.8%	38.5%
p-value	1	**0.001**	1.00	0.29	0.89	0.45	1	0.20	0.87	0.76	1	**0.028**	1	0.89	0.51	0.77	0.78	0.88	**0.0001**	1	0.38

Table 3 Comparison of best corrected visual acuity (BCVA) over time, measured in Snellen and expressed as a percentage.

Table 3 shows the proportion of eyes achieving different degrees of visual acuity over time. At 3 months postoperatively, more eyes in the DMEK group achieved a visual acuity of≥ 20/25 (31.5% vs 12.0%, p = 0.001), but this difference was lost at 6 and 12 months. At 24 months, most patients still retained ≥ 20/40 vision in both groups (68.3% in the UT-DSAEK group vs 70.5% in the DMEK group, p = 0.76), although with a higher proportion of patients with ≥ 20/20 vision in the DMEK group (12.2% in the UT-DSAEK group vs 25.0% in the DMEK group, p = 0.028). The improvement in visual acuity was sustained over the 5-year follow-up, with a higher percentage of patients achieving a visual acuity of≥ 20/40 among those who underwent DMEK (59.1% for UT-DSAEK vs 84.6% for DMEK, p = 0.0001).

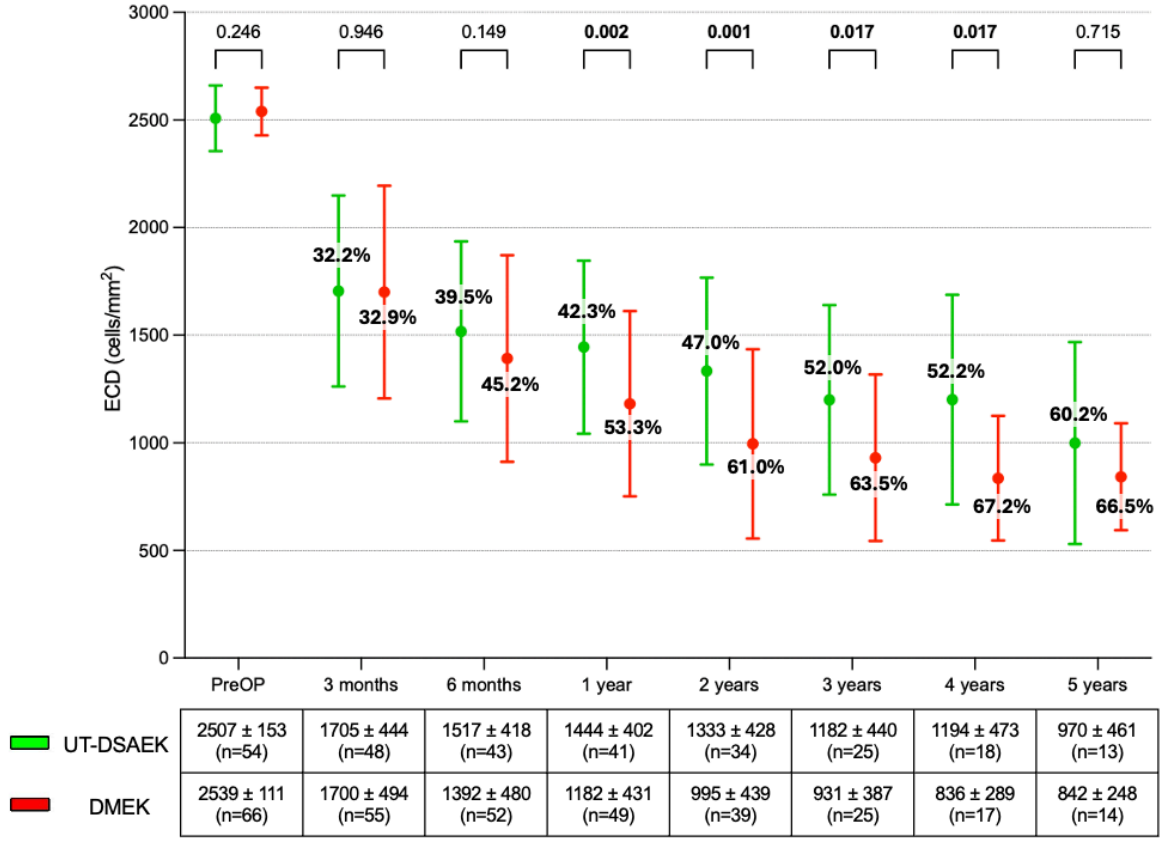
Endothelial Cell Density and Cell Loss Comparison

Figure 14 illustrates the progressive loss of endothelial cells observed in both groups during the follow-up.

In the UT-DSAEK group, donor ECD was 2507 ± 153 cells/mm² and decreased to 1444 ± 402 (-42.3% ECL) and to 970 ± 461 cells/mm² (-60.2% ECL) at 1 and 5 years of follow-up, respectively. Similarly, the DMEK group experienced a significant decrease in ECD, from a preoperative mean of 2539 ± 111 cells/mm² to 1182 ± 431 cells/mm² (-53.3%) at 1 year postoperatively, which further declined to 842 ± 248 cells/mm² (-66.5%) at 5 years.

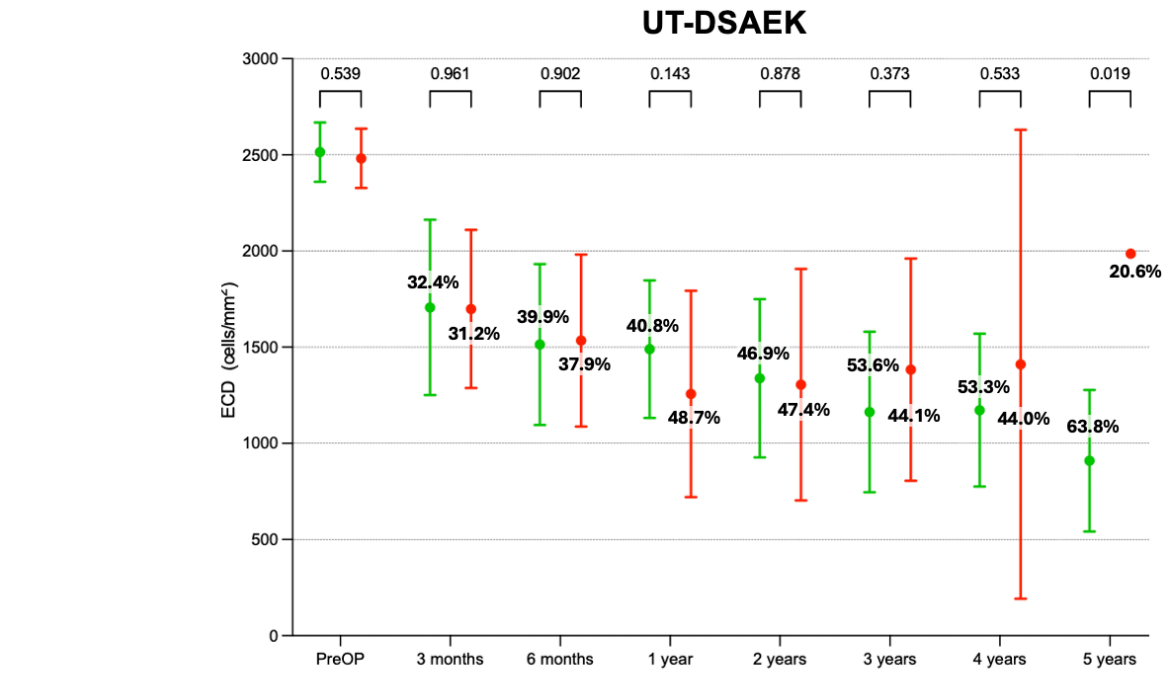
Whilst no significant difference was found between the two groups in the first 12 postoperative months and at the last follow-up visit, the DMEK group exhibited a significantly lower ECD compared to UT-DSAEK between 1 and 4 years postoperatively ($P < 0.05$).

As shown in Figure 15, patients undergoing UT-DSAEK for a failed DSAEK graft exhibited comparable endothelial cell loss and similar ECD at all follow-up visits ($p > 0.05$) regardless of prior immune endothelial rejection episodes.



	PreOP	3 months	6 months	1 year	2 years	3 years	4 years	5 years
UT-DSAEK	2507 ± 153 (n=54)	1705 ± 444 (n=48)	1517 ± 418 (n=43)	1444 ± 402 (n=41)	1333 ± 428 (n=34)	1182 ± 440 (n=25)	1194 ± 473 (n=18)	970 ± 461 (n=13)
DMEK	2539 ± 111 (n=66)	1700 ± 494 (n=55)	1392 ± 480 (n=52)	1182 ± 431 (n=49)	995 ± 439 (n=39)	931 ± 387 (n=25)	836 ± 289 (n=17)	842 ± 248 (n=14)

Figure 14 ECD comparison between UT-DSAEK and DMEK. ECL is expressed as a percentage of the initial donor ECD and stated above each ECD box plot graph.



	PreOP	3 months	6 months	1 year	2 years	3 years	4 years	5 years
Without PreOP Rejection	2514 ± 154 (n=43)	1707 ± 456 (n=39)	1514 ± 418 (n=35)	1490 ± 358 (n=33)	1338 ± 412 (n=28)	1163 ± 417 (n=20)	1173 ± 397 (n=15)	909 ± 368 (n=11)
With PreOP Rejection	2482 ± 154 (n=11)	1699 ± 411 (n=9)	1534 ± 447 (n=8)	1257 ± 537 (n=8)	1305 ± 602 (n=5)	1383 ± 578 (n=4)	1411 ± 1219 (n=2)	1986 ± 0 (n=1)

Figure 15 ECD comparison between UT-DSAEK patients with and without previous history of immune endothelial rejection. ECL is expressed as a percentage of the initial donor ECD and stated above each ECD box plot graph

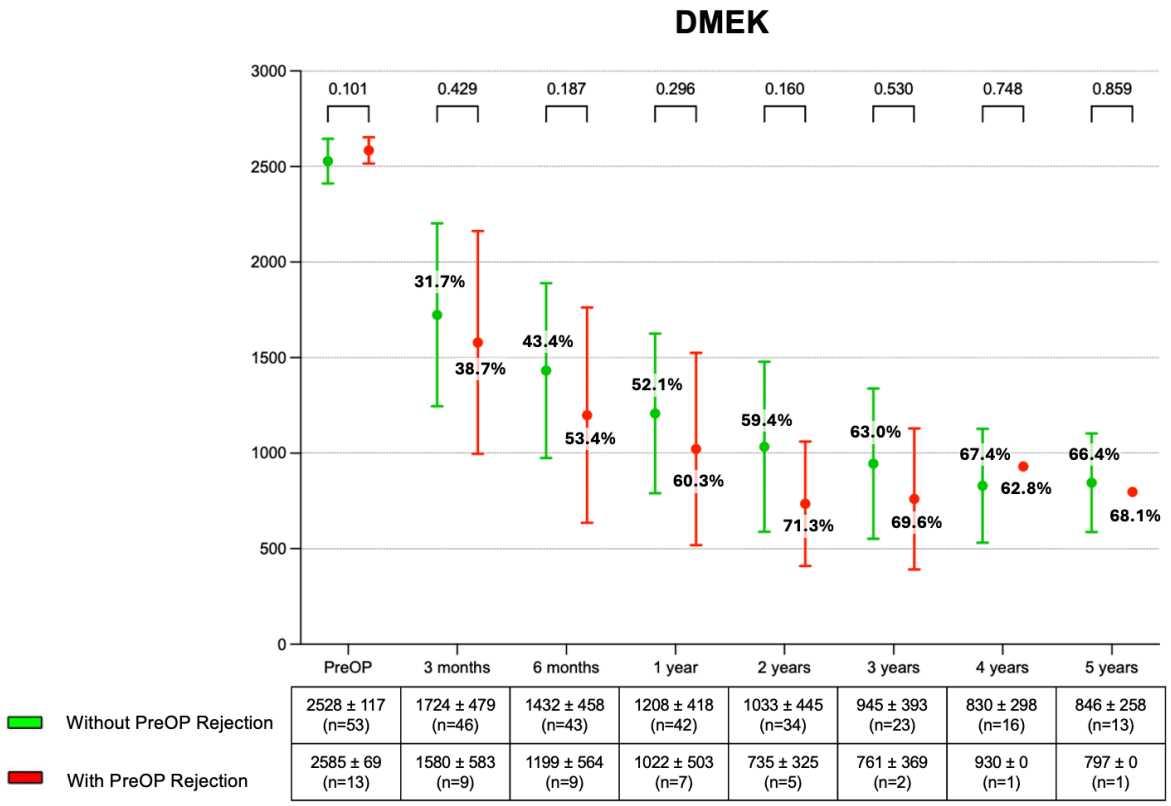


Figure 16 ECD comparison between DMEK patients with and without previous history of immune endothelial rejection. ECL is expressed as a percentage of the initial donor ECD and stated above each ECD box plot graph

An analogous subgroup analysis was also conducted in the DMEK cohort, which consistently yielded no significant difference in ECD and ECL between patients with and without a history of endothelial rejection, as illustrated in Figure 16.

Graft Survival Comparison

Overall, 18 cases (33.3%) in the UT-DSAEK group experienced graft failure within 5 years of follow-up, compared to 22 (33.3%) patients among those who underwent DMEK (p = 1.00).

Among patients who developed graft decompensation, 9 (50%) in the UT-DSAEK group and 10 (45.5%) in the DMEK group experienced an episode of immune endothelial rejection (p = 1.00).

In the remaining cases, graft decompensation was attributed to non-immunologic late endothelial failure. No occurrence of primary graft failure was observed in our cohort.

In the UT-DSAEK group, Kaplan-Meier cumulative graft survival probabilities at 1, 2, 3, 4, and 5 years were 94.3%, 84.9%, 79.7%, 67.9%, and 52.5%, respectively; while in the DMEK group were 86.3% at 1 year, 79.6 % at 2 years, 73.4% at 3 years, 58.9% at 4 years, and 54.7% at 5 years, with no statistically significant difference (log-rank p = 0.62).

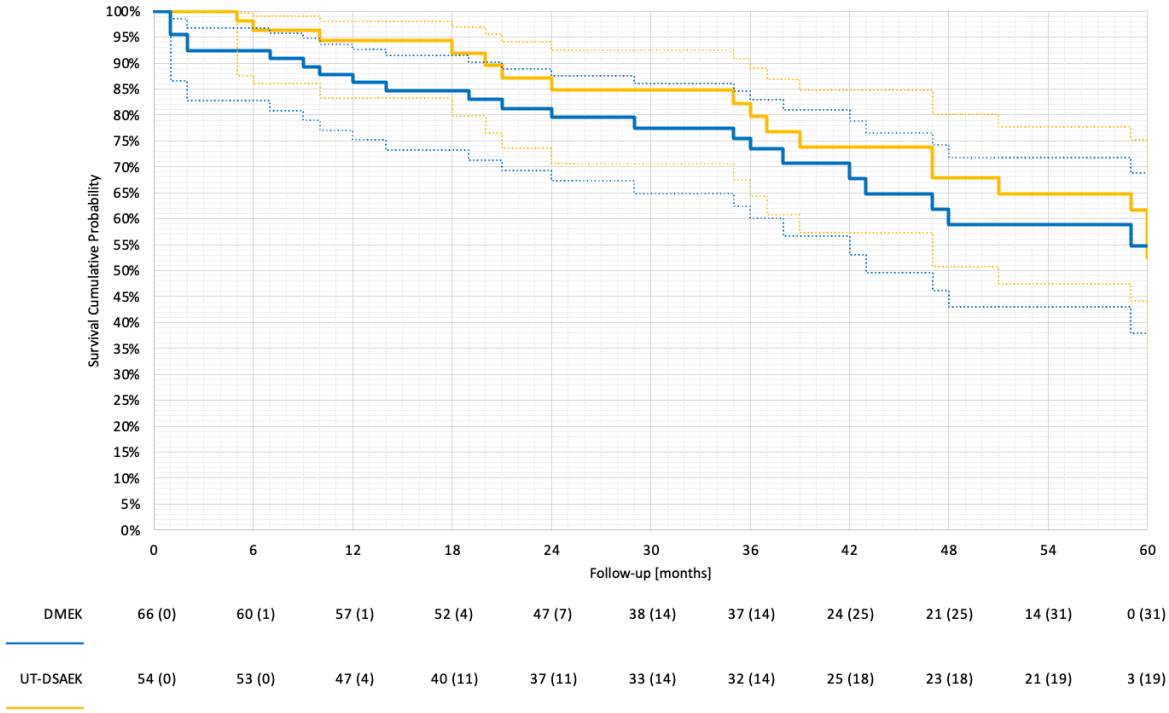


Figure 17 Kaplan–Meier graft survival curves of patients after UT-DSAEK and DMEK for failed DSAEK

Similar results were observed in the subgroup analysis stratified for prior immune endothelial rejection.

UT-DSAEK patients without a history of immune-mediated endothelial impairment showed cumulative survival probabilities of 95.3%, 89.2%, 85.8%, 74.6%, and 55.0% at 1, 2, 3, 4, and 5 years, respectively. In contrast, UT-DSAEK patients who experienced endothelial rejection in their previous graft demonstrated lower survival rates, with cumulative probabilities of 90.1%, 70.7%, 60.6%, 45.5%, and 45.5% at the same timepoints. However, the difference did not reach statistical significance (log-rank p = 0.29).

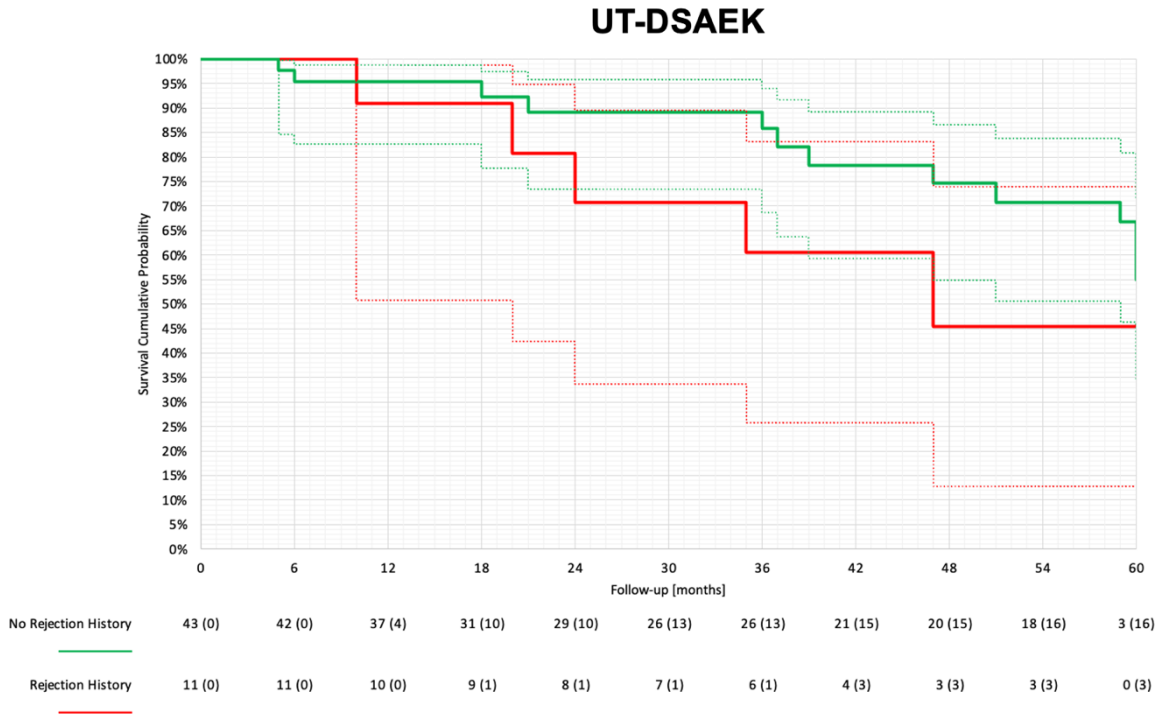


Figure 18 Kaplan–Meier graft survival curves of UT-DSAEK patients with and without a history of immune endothelial rejection in the previous graft

On the opposite, the same subgroup analysis in the DMEK cohort resulted in significantly higher (log-rank p = 0.03) graft survival at 1 year (86.6 vs 84.6%), 2 years (84.5 vs 58.0%), 3 years (79.6 vs 46.5%), 4 years (66.0 vs 23.2%), and 5 years (60.9% vs 23.2%).

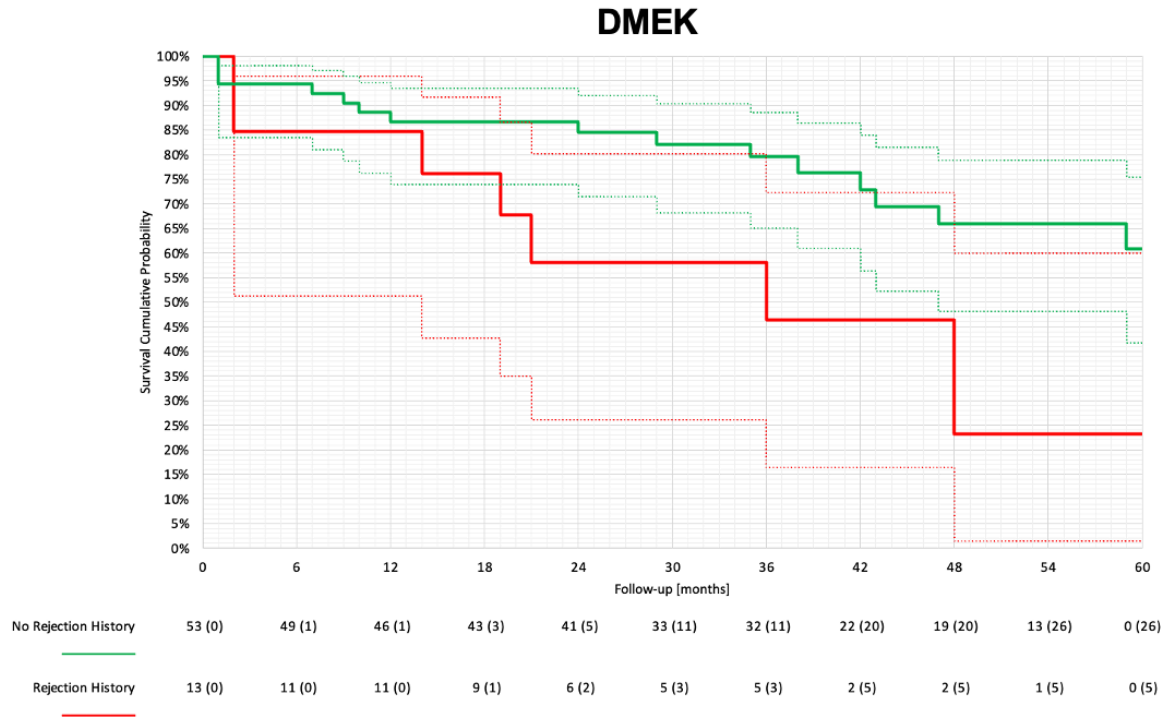


Figure 19 Kaplan–Meier graft survival curves of DMEK patients with and without a history of immune endothelial rejection in the previous graft

5. DISCUSSION

In the past 20 years, corneal transplantation has undergone dramatic improvements. Compared to PK, lamellar endothelial keratoplasty techniques have enabled faster visual recovery, lower astigmatism, and a reduced risk of rejection.

From their introduction at the beginning of the century, the increasing popularity and advantages of these procedures over PK have led to a high number of EKs performed each year, which justifies the high number of failed grafts seen in recent years.

Since its first description, DMEK has been considered a technical advancement over DSAEK, offering faster and better visual recovery, with a lower risk of rejection, despite higher rates of perioperative complications such as primary graft failure, rebubbling, and a longer learning curve.

However, as DSAEK grafts have evolved towards the thinner lamellae used in UT-DSAEK, the differences in outcomes started to fade, highlighting the need for further research and debate. [53]

Moreover, in complex eyes such as those with previous eye surgery, the technical difficulties associated with DMEK could overweight its possible benefits over UT-DSAEK.

In our study, we compared the BCVA, ECL, graft survival, and rejection rate of UT-DSAEK and DMEK up to 5 years of follow-up in eyes with a failed DSAEK, and investigated whether a previous history of endothelial immune rejection could influence any of these outcomes.

Currently, most of the literature that compares DMEK's and UT-DSAEK's outcomes for treating graft decompensation involves failed PK grafts and is therefore not directly comparable to our data. [54,55]

There are only a limited number of reports, with a non-comparative design, documenting the outcomes of either DMEK or UT-DSAEK in eyes with previous failed DSAEK procedures, which will be compared with our findings.

Moreover, as some reports suggest, primary and secondary EK procedures might yield similar results. Based on this assumption, comparisons were also made with studies on primary DMEK and UT-DSAEK. [56,57]

In our case series, both UT-DSAEK and DMEK showed a significant and stable improvement in BCVA postoperatively. At 1 year postoperatively, patients achieved a

mean BCVA of 0.24 ± 0.22 logMAR and 0.26 ± 0.27 logMAR in the UT-DSAEK and DMEK groups, respectively, aligning with previous reports of secondary EK for failed DSAEK. In their series of 15 eyes undergoing DMEK for DSAEK failure, Weller et al. achieved a mean BCVA of 0.23 ± 0.21 logMAR postoperatively. [57]

Similarly, Busin et al. reported a postoperative BCVA of 0.34 ± 0.49 logMAR after repeated DSAEK. [56]

When considering primary EK procedures, Chamberlain et al. reported that DMEK provides superior visual outcomes compared to UT-DSAEK as early as 3 months and up to 1 year after surgery. [58]

However, the apparent superiority of DMEK could be attributed to a selection bias in the inclusion criteria, such as the enrollment of triple procedures or bilateral surgeries, which may have influenced the impact of endothelial keratoplasty on visual acuity. Considering a study with more rigorous eligibility criteria, such as the comparison between UT-DSAEK and DMEK published by Dunker et al., no statistically and clinically significant differences were found between the two techniques. [59]

Regarding the speed of visual recovery, previous reports have found that UT-DSAEK may take up to twice as long to achieve a stable and definitive visual recovery compared to DMEK. [60,61]

In our study, however, a similarly rapid visual recovery was achieved in both UT-DSAEK and DMEK. The lack of significance we observed in both the amount and speed of visual recovery may suggest that the benefits of DMEK are offset by factors related to eyes that have previously undergone graft failure. When considering post-EK visual performance, it is crucial to consider the preoperative condition of the host cornea. Eyes undergoing regrafting typically present poor anterior chamber visibility, stromal alterations from chronic edema, or complex anatomical characteristics. These conditions may limit the visual potential regardless of the graft type and may also increase the risk of overmanipulation during DMEK.

Furthermore, in our cohort, the time between the first DSAEK and the secondary procedure was significantly longer in the DMEK group, suggesting that these patients may have experienced longer-standing edema and greater changes in corneal anatomy, requiring a longer recovery period than primary EK and potentially limiting the final visual outcome.

However, no differences in BCVA were observed between the two groups, neither preoperatively nor at 60 months after surgery, and the percentage of eyes achieving 20/25 vision or better was comparable in both groups (UT-DSAEK 54.5% vs DMEK 53.8%, p =

1.00). This aligns with prior observations that UT-DSAEK approaches the visual performance of DMEK when the stromal component is minimized, particularly when the thickness is less than 70 µm. [61]

Another major factor determining the performance of an endothelial keratoplasty is the loss of endothelial cells over time. In our study, both groups achieved comparable ECLs at 3 and 6 months, indicating that the initial surgical trauma and early postoperative course may not differ significantly. However, UT-DSAEK patients started to exhibit a significantly lower ECL compared to DMEK patients from 1 year (UT-DSAEK 42.3% vs DMEK 53.3%, p = 0.002) up to 4 years of follow-up (UT-DSAEK 52.2% vs DMEK 67.2%, p = 0.017), although with a comparable ECL between each year of approximately 5-7%.

Our results suggest that, in addition to the well-known differences in intraoperative handling, the graft types may also adapt differently to eyes with a history of previous surgery. In the presence of altered anterior segment anatomy and host interface, erratic inflammatory environment, and unstable intraocular pressure, the stromal-supported UT-DSAEK lamella may provide a more resilient scaffold for the endothelium over time than the bare Descemet membrane used in DMEK grafts.

The lack of difference in ECL at 5 years may be biased by the selective dropout of the most compromised grafts, thereby attenuating intergroup differences among surviving eyes.

Overall, our results are consistent with other studies on secondary UT-DSAEK and DMEK for failed DSAEK, and they exhibit a higher ECL compared to primary EKs. [64,65]

Various hypotheses have been proposed to explain the higher rate of ECL observed in secondary EK. For instance, eyes that have undergone prior surgeries may require more extensive intraoperative graft manipulation due to poor visualization of the anterior chamber. Additionally, the steroid-induced increase in intraocular pressure may accelerate cell loss. Finally, previously transplanted eyes lose their immune-privileged status and are exposed to an immune system already sensitized to corneal antigens.

Further supporting this observation, we observed a cumulative rejection rate after 5 years of follow-up of 16.6% and 15.2% in the UT-DSAEK and DMEK groups (p = 0.99), significantly higher compared to those associated with primary EKs

Wakimasu et al. and Madi et al. reported rejection rates of 5.4% and 6.9%, respectively, for UT-DSAEK at 5 years. [65,66] Regarding DMEK, Birbal and colleagues reported a 5-year

cumulative rejection rate of 2.8% in their series of 500 eyes, similar to the 4% rejection rate reported by Vasiliauskaité et al. 10 years following primary DMEK. [67,43]

Analogously, in our study, the cumulative graft survival probability was significantly lower than that of primary EKs. Price et al. reported a 5-year graft survival rate of 93% after primary DSAEK. [68] In a separate study, Woo et al. reported that the graft survival rate at 5 years was 78.4% and 97.4% after primary DSAEK and DMEK, respectively. [50]

Overall, our results are consistent with the concept that a history of corneal graft failure represents a high-risk factor for accelerated ECL, immune rejection, and reduced long-term graft survival. However, the exact mechanisms underlying this association remain poorly understood, and the available literature offers contradictory evidence and interpretations. Notably, our subgroup analysis revealed almost no statistically significant differences between eyes with and without a history of endothelial rejection in terms of ECL, rejection rates, or graft survival, suggesting that once the failed graft is exchanged with a new lamella, prior immune events may have a more limited long-term impact than previously assumed.

Several limitations should be considered when interpreting the results of this study. For instance, its non-randomized design may have introduced a selection bias. Moreover, the longer interval between the primary DSAEK and the secondary EK in the DMEK group may have led to more prolonged edema or chronic inflammatory changes, potentially affecting the outcomes of this group. Importantly, attrition increased over the later years, reducing the available sample size at the last visits, potentially attenuating differences between groups, particularly for ECL, where selective dropout of the most compromised grafts could have biased late outcomes. Lastly, the monocentric design of this study limits the generalizability of our findings to centers with different levels of surgical expertise.
Prospective, randomized, multicenter studies with standardized inclusion and surgical criteria and longer follow-up are needed to determine the superiority of one technique for treating failed DSAEK grafts.

In conclusion, to the best of our knowledge, this is the first study to directly compare UT-DSAEK and DMEK for the management of failed DSAEK grafts. Both techniques achieved comparable visual outcomes and graft survival rates throughout follow-up, despite a tendency toward greater endothelial cell loss in the DMEK group over time.

Notably, the rate of endothelial rejection in both groups was higher than usually reported for primary EKs but did not differ between eyes with and without a previous history of endothelial immune rejection, highlighting the increased vulnerability of eyes undergoing repeat keratoplasty.

Our findings indicate that, in cases of DSAEK failure, the long-term performance of both techniques tends to align. Consequently, the selection of the procedure should be primarily influenced by anatomical considerations and surgical preference, rather than by the assumed superiority of one technique over the other.

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