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The Evolution of Endothelial Therapeutics

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Introduction

Corneal endothelial diseases comprise a spectrum of conditions that critically affect the health and transparency of the cornea, posing unique challenges for ophthalmologists. The most prevalent among these is Fuchs' endothelial corneal dystrophy (FECD), which accounts for approximately 39% of all corneal transplants globally.[1] Bullous keratopathy (BK) can affect the entire cornea, leading to painful blisters that may become infected. Other rarer pathologies, such as iridocorneal endothelial syndrome, posterior polymorphous corneal dystrophy, and congenital hereditary endothelial dystrophy, present unique diagnostic and therapeutic challenges. Additionally, graft failure remains a notable indication for treatment. High-risk cases experience failure rates exceeding 35% within 3 years, with endothelial rejection accounting for half of the cases.[2] Corneal transplants have been considered the gold standard for decades, with advancements in surgical techniques leading to shorter operating times, faster visual recovery, and improved outcomes. However, the growing global shortage of transplant-grade donor tissue further complicates treatment, underscoring the urgent need for innovative approaches such as genetic and cell-based therapies.

Historical Review of Treatment

Penetrating Keratoplasty

For decades, penetrating keratoplasty (PK) was the mainstay of surgical treatment for corneal endothelial disease. However, postoperative complications can be significant, ranging from suture-related issues, delayed wound rupture, and corneal transplant failure. Moreover, surgically induced astigmatism is an important consideration for these patients. Those with bilateral disease often experience a prolonged waiting period between surgical intervention in each eye given the lengthy visual recovery time after PK. Given these disadvantages, there has been much interest in surgical methodologies that could focus solely on replacing the endothelium.

Endothelial Keratoplasty

The most significant evolution in therapy for endothelial diseases over the past 25 years has been the transition from full-thickness PK to selective transplantation of the endothelial layer. The origins of posterior lamellar keratoplasty date back to the 1950s, and in 1998, an intrastromal approach was proposed.[4] Although not widely adopted due to its surgical complexity, an era of innovation in endothelial keratoplasty (EK) techniques followed. The subsequent adaptation, deep lamellar endothelial keratoplasty (DLEK), integrated the use of viscoelastic to stabilize the anterior chamber amongst other modifications.[5] This was followed by Descemet-stripping endothelial keratoplasty (DSEK) and later Descemet-membrane endothelial keratoplasty (DMEK), which solidified EK as the treatment of choice for endothelial disease.[6]

DSEK involves replacing the host endothelium with a donor graft of endothelial and stromal tissue. Descemet stripping automated endothelial keratoplasty (DSAEK) is a subsequent advancement that includes the use of a microkeratome to cut the donor tissue. Compared to PK, DSAEK consistently results in less astigmatism, better wound stability, and faster visual recovery.[7] In DMEK, only the endothelium and its carrier Descemet's membrane are replaced with donor tissue, resulting in a much thinner graft. Both DSAEK and DMEK require removal of the host endothelium via a procedure called descemetorhexis, which can be achieved either manually or, less frequently, with a femto-second laser.[8]

In most countries with ready access to tissue and the ability to navigate a surgical learning curve, a shift toward DMEK has been observed for the majority of endothelial grafts.[9,10] Indeed, DMEK has become the gold standard for treating endothelial failure, with faster visual recovery, higher rates of 20/20 acuity, and the lowest rates of rejection.[11] Over a 10-year study period, DMEK showed the lowest median endothelial cell loss (63%), followed by DSEAK (68%), then PK (76%). Similarly, in terms of graft survival, a large series found that the cumulative risk of graft failure over 10 years was lowest with DMEK, followed by DSAEK, then PK.[7]

DMEK surgery presents technical challenges related to graft manipulation, particularly in the absence of an iris scaffold or deep chamber, as well as having a higher rebubbling rate. An uncommon but important intraoperative complication is fibrin release from the iris, which may have deleterious effects on endothelial corneal dystrophy (ECD) and graft survival. Anticoagulant use has been implicated as a risk factor alongside surgical trauma to vascular tissues and prolonged surgical manoeuvres. To mitigate this issue, strategies such as using heparin in the balanced salt solution infusion or tissue plasminogen activator (tPA), borrowed from veterinary and pediatric ophthalmic surgery, are being studied for their potential benefits.[12]

Finally, newer techniques for tissue preparation have emerged to address the technical challenges of DMEK surgeries by using DSAEK-like tissue preparation methods. In ultrathin-DSAEK (UT-DSAEK), donor grafts of approximately <110–100 µm thickness are transplanted, which are thinner than the traditional DSAEK's 150 µm and thicker than DMEK's average 10–15 µm thickness. UT-DSAEK displayed superior visual acuity outcomes compared to DSAEK in a large case series and randomized controlled trial without increasing the risk of graft detachment.[14] The term "nanothin" DSAEK (NT-DSAEK) is used to describe grafts achieving a thickness of ≤50 µm, but more studies are needed to evaluate the benefits of this technique.[15]

Descemet-Stripping Only

Descemet-stripping only (DSO), also known as Descemetorhexis Without Endothelial Keratoplasty (DWEK), has emerged as a surgical option for select cases of FECD. The primary indication for DSO is the presence of symptomatic central guttae and a clear peripheral cornea with an ECD >1000 cells/mm^2 (if measurable).[16] In DSO, the diseased endothelium and underlying Descemet's membrane are removed without subsequent transplantation **(Figure 1)**. The proposed mechanism for central corneal clearing is corneal endothelial cell (CEC) migration from the periphery to repopulate the endothelium. As a transplant-free approach, DSO avoids the surgical challenges associated with EK, including intracameral gas or air management, graft attachment complications, and rejection. However, this intervention has limitations, including prolonged visual recovery, and the possibility of subsequent surgeries.[17]

Originally described by Paufique in 1955, DSO has undergone a modern renaissance.[18] Recent studies have shown promising but somewhat unpredictable early results. While some cases have required subsequent EK, others have demonstrated complete resolution of corneal edema with improvement in best corrected visual acuity (BCVA) for reasons that were initially unclear.[19]

Recently, research in this area has shifted to investigate surgical factors that contribute to successful corneal clearance following DSO. Laboratory studies and medium-sized clinical trials have confirmed that surgical factors including descemetorhexis size and technique may contribute to differences in outcomes following DSO.[16] It is now accepted that limiting the descemetorhexis size to less than 5 mm, employing a peeling rather than scoring technique, and the addition of topical Rho-kinase (ROCK) inhibitors are proven strategies to improve the likelihood of DSO success, which now exceeds 90%.[17,20]

Emerging Therapies

Corneal transplantation remains the sole effective treatment for FECD. Nevertheless, modern EK techniques are not without complications. They are associated with a 28.8% allograft detachment rate and a 1.7% rate of primary graft failure during the immediate postoperative period, often requiring additional surgical interventions.[21] Long-term outcomes reveal graft failure rates of 3.8–5% at 5 years in specialized, single-centre settings. Furthermore, nearly 25% of patients develop glaucoma following EK, necessitating further medical or surgical management.[22] Globally, the limited availability of tertiary-care corneal transplant surgeons, along

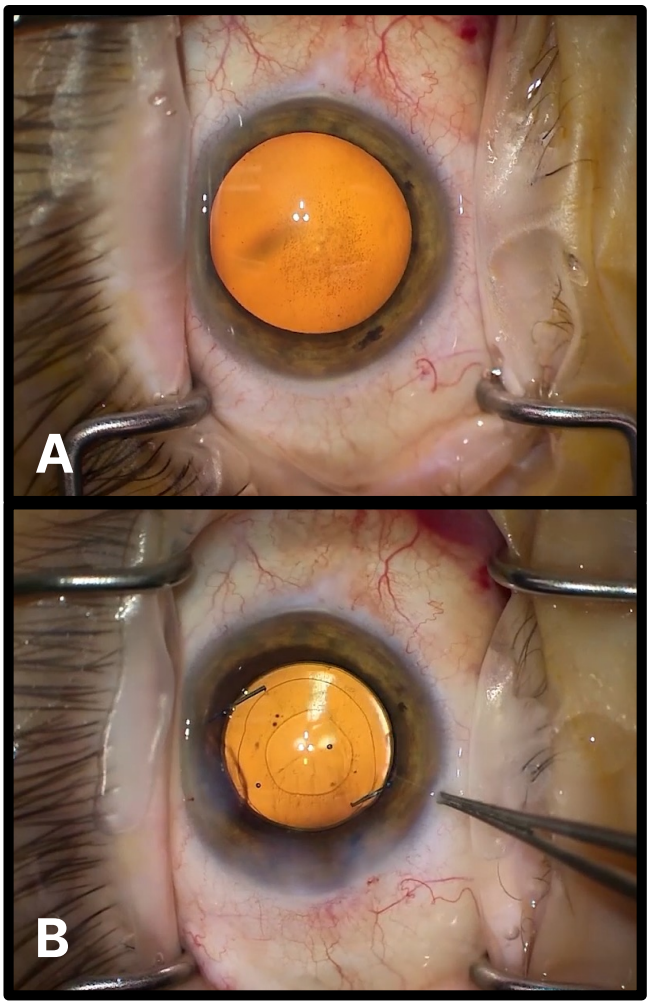

Figure 1. Surgeon's view of Descemet-stripping only (DSO) combined with phacoemulsification. **(A)** Preoperative view with eyelid speculum in place; **(B)** Postoperative view demonstrating the completed larger capsulorhexis and smaller descemetorhexis, with a 3-piece lens in the bag; *courtesy of Greg Moloney, MBBS (Hons), BSc(Med), MMed, FRANZCO, FRCSC, Antoine Sylvestre-Bouchard, MD, MSc., and Mary Holdsworth, MD, BSc, MScPH*

with insufficient donor tissue and eye banking infrastructure, restricts the accessibility of EK, emphasizing the urgent need for innovative treatment alternatives **(Table 1)**.

ROCK Inhibitors

Rho-associated coiled-coil containing protein kinases (ROCKs) are involved in cytoskeleton organization, cell migration, cell-cell adhesion, proliferation, cell cycle control, and apoptosis. ROCK inhibitors, by extension, have been shown to promote cell adhesion, inhibit apoptosis, and increase proliferation of CECs.[23] Based on these promising studies, the use of topical and injectable ROCK inhibitors has increased in recent years. For instance, topical Y-27632 and ripasudil have been shown to promote corneal endothelial wound healing and improve corneal edema in BK and FECD patients. Additionally, both Y-27632 and ripasudil have been successfully applied as salvage agents in cases of DWEK where the cornea failed to clear.[16] Most recently, a review of the role of ROCK inhibitors in corneal disease found that Y-27632, ripasudil, and netarsudil were all beneficial in promoting endothelial healing.[24] The primary mechanism of benefit appears to be the accelerated closure of endothelial defects, with well-demonstrated anti-apoptotic effects as well.[23]

Tissue-Engineered Grafts and Injected Cell Suspensions

With the global corneal donor shortage, there is a strong incentive to explore technologies that not only enhance but also replicate and/or replace the corneal endothelium. This can be achieved by leveraging tissue engineering modalities, such as Tissue-Engineered Endothelial Keratoplasty (TE-EK), and the injection of cell suspensions of cultured human CECs. Cultivating human CECs presents unique challenges, particularly to do with a low proliferative potential, rapid cellular senescence, and a tendency to undergo endothelial-to-mesenchymal transition. Fundamentally, TE-EK involves seeding human CECs onto a scaffold carrier, with various types of scaffolds having been investigated. The resulting endothelial sheet is then transplanted into the recipient's eye in a fashion similar to DSAEK. To date, several studies using animal transplantation models have shown that these endothelial sheets are functional in vivo, with similar morphology to native corneal endothelium.[25,26] Research groups have now progressed to human trials investigating TE-EK for conditions such as FECD or BK.

Studies investigating the delivery of cultured human CECs as a cell suspension have produced promising results, showing the formation of an endothelial monolayer and functional corneal endothelium.[27] The addition of ROCK inhibitors in these studies produced superior outcomes, presumably by enhancing adhesion and cell engraftment. A landmark clinical trial of patients with BK demonstrated that descemetorhexis followed by direct injection of human CECs and ROCK inhibitor, led to improved ECD in all 11 treated eyes. Improvements in BCVA and central corneal thickness were also reported

Contemporary		Emerging	
Penetrating Keratoplasty		**Pharmacologic Therapies**	ROCK inhibitors Antioxidants Fibroblast Growth Factor
Endothelial Keratoplasty		**Cell-Based Therapies**	Tissue-Engineered EK Cell Suspension Injections
DMEK			
DSAEK	UT-DSAEK NT-DSAEK	**Genetic Therapies**	Antisense oligonucleotides CRISPR
DSO			

Table 1. The Evolution of Endothelial Therapeuthic Options; *courtesy of Greg Moloney, MBBS (Hons), BSc(Med), MMed, FRANZCO, FRCSC, Antoine Sylvestre-Bouchard, MD, MSc., and Mary Holdsworth, MD, BSc, MScPH*

Abbreviations: DMEK: Descemet-membrane endothelial keratoplasty; **DSAEK:** Descemet stripping automated endothelial keratoplasty; **DSO:** Descemet-stripping only; **EK:** endothelial keratoplasty; **NT-DSAEK:** nanothin-DSAEK; **ROCK:** Rho-associated coiled-coil containing protein kinases; **UT-DSAEK:** ultrathin-DSAEK

in most eyes. Importantly, there were no major complications reported, and the improvements in corneal clearance and BCVA were sustained beyond 3 years in most cases.[28]

Antisense Oligonucleotides

Antisense oligonucleotides (ASOs) represent a promising avenue for the treatment of FECD with underlying trinucleotide repeat mutations. These short, synthetic, single-stranded oligodeoxynucleotides exert their effects by modifying RNA activity, enabling the reduction, restoration, or alteration of protein expression. Recent advancements in ASO pharmacology have accelerated their clinical translation, with two ASO therapies already approved by the US Food and Drug Administration (FDA) for conditions such as Duchenne muscular dystrophy and spinal muscular atrophy.[29]

The potential for treating FECD has been transformed by the discovery that expansions at the intronic CTG18.1 triplet repeat polymorphism of *TCF4* (MIM 602272) account for 70% of FECD cases in the United States. This finding establishes FECD as the most common repeat expansion disorder in humans.[30] *TCF4* expansions of greater than 40 CTG repeats confer a significant risk for developing FECD. In FECD endothelial tissue, expanded CUG-repeat RNA transcripts accumulate as nuclear foci that can be visualized by fluorescent in-situ hybridization. These nuclear foci ultimately sequester splicing factors and impair the splicing process.[31]

Subsequently, ASOs targeting this CTG18.1 repeat expansion in *TCF4* have been designed and investigated with results suggesting reduced RNA toxicity.[30] However, further application of ASOs in the clinic requires optimization of ASO delivery, target engagement, and safety profiles.[29] Current data suggests that in vivo delivery of ASOs to corneal tissue through intraocular injection (intracameral or intravitreal) is a feasible and effective method for regulating gene expression.

CRISPR

As our understanding of genetic mutations in corneal endothelial disease has expanded, the possibility of genome editing with CRISPR/Cas9 to target known mutations has surfaced. CRISPR/Cas9-mediated genome editing has been described in cultured human CECs and in murine models with *Col8a2* missense mutations. To date, no studies have demonstrated gene editing of the more common CTG repeats in *TCF4*. While there is enormous therapeutic potential, including the possible prevention of corneal endothelial disease

pathogenesis, challenges include the delivery method, delivery vector choice, and specific targeting.[32]

Antioxidants

Although FECD is a complex disease with several different primary mechanisms involved, secondary mitochondrial dysfunction and mitophagy play a central role in the decline of endothelial cell viability during the progression of this disease. The rationale behind antioxidant therapies rests on the premise that the oxidative response pathways are dysfunctional in patients with endothelial disease. Oxidative stress leads to dysregulated apoptosis of CECs. By targeting this dysfunctional response with free radical scavengers to mitigate the accumulation of reactive oxygen species, the aim is to improve the survival of CECs.[33]

FECD pathogenesis is also linked to environmental ultraviolet A (UVA) exposure. UVA exposure contributes to iron-mediated lipid peroxidation (ferroptosis) and CEC death in FECD. Experimental evidence shows that both iron chelation and anti-ferroptosis antioxidant treatments can prevent cell death in FECD cell cultures. Solubilized ubiquinol, the active form of Coenzyme Q10, has been shown to prevent cell death caused by RSL3-induced ferroptosis, suggesting a potential role for anti-ferroptosis therapies in FECD.[34]

Conclusion

Over the past few decades, corneal endothelial treatments have significantly evolved, transitioning from advancements in partial thickness keratoplasty to tissue-sparing, transplant-free innovations. While challenges such as global donor tissue shortages and postoperative complications persist, developments in cell-based therapies, tissue engineering, and molecular approaches are expanding treatment options and accessibility. If recent history is any indication, ongoing research will continue to propel endothelial disease treatment forward, restoring vision and improving quality of life.

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