INTRODUCTION

It is quite remarkable how far we have come from the early days of corneal transplantation for our Fuchs dystrophy patients. Some may remember a time when the standard of care was penetrating keratoplasty (PKP), a procedure that involved using numerous sutures and would frequently result in irregular astigmatism. The healing time was long and burdensome for our elderly patients and most would still sustain a high refractive error unable to see well with glasses. It was unimaginable at the time that perfect visual acuity could be attained. However, the year of 1998 revolutionized our future, paving the way for improving patient outcomes and safety at an unprecedented pace.

During this year, Melles et al introduced a surgical technique in which a stromal pocket was made across the cornea through an 8.0 mm limbal incision. A posterior lamellar disc was resected and replaced by a donor posterior disc. This technique showed minimal post-operative topographic changes and innovatively used air bubble to support transplanted tissue without sutures. It was at this time the modern era of endothelial transplantation began. Two years later, Terry et al performed a slightly modified version of Melles’ procedure for the first time in the United States. He did this by introducing an artificial anterior chamber to create donor grafts that accommodated the standard...
corneoscleral donor tissue supplied by US eye banks and stabilizing the recipient anterior chamber by the use of viscoelastic. This modified technique was named deep lamellar endothelial keratoplasty (DLEK). Even though this technique improved visual outcomes with a speedier recovery, the tedious and risky manual preparation of both recipient bed and donor graft prevented it from becoming popular.

**Historical Overview**

In 2004, Melles et al. described the concept and technique to create recipient stromal bed by excising only the Descemet membrane. Termed “descemeterohexis”, this breakthrough eliminated the obstacle of manual dissection and resection of recipient stroma. Later in 2005, Price et al. further modified descemeterohexis by using different surgical instruments and renamed the evolved procedure as Descemet stripping endothelial keratoplasty (DSEK). However, when microkeratome was used in the early patients to prepare donor grafts, the evolved procedure was renamed Descemet stripping automated endothelial keratoplasty (DSAFEK) by Gorovoy - primarily to emphasize the automated microkeratome dissection of the donor graft. The clinical trial carried by Price et al comparing outcomes of microkeratome dissected and manually dissected donor tissue demonstrated reduced donor tissue perforation risk, improved visual outcomes, and promoted the utilization of microkeratome for donor graft preparation. Subsequently, eye banks started to provide precut donor tissue for DSAFEK procedures, especially when several comparative trials supported that eye bank precut tissue worked equally as well as surgeon dissected tissue. This quickly displaced the painstaking procedure of manual dissection and led to automated dissection as the gold standard.

At the time it was believed that the major obstacles in DSAFEK evolution had been overcome. It soon gained worldwide popularity and became the mainstay of treatment for endothelial dysfunction. In the report by American Academy of Ophthalmology evaluating safety and outcomes, evidence showed that compared to penetrating keratoplasty (PK), DSAFEK was superior in terms of early visual recovery and refractive stability, postoperative refractive outcomes, and wound and suture-related complications. Given this, there was a shifting downward trend of preferred keratoplasty from 2005 to 2014. In this time period, the proportion of PK in total corneal transplants decreased from 95% to 42%, while DSAFEK increased to 50%, and became the most commonly performed corneal transplantation in the US in 2014.

Despite the superior outcomes with DSAFEK, even further modification remained to take place. During the evolution, Neff et al. noticed and addressed the issue of donor graft thickness. They found graft thickness to be an influential factor in final visual outcomes. The patients with postoperative grafts thinner than 130 µm had better visual outcomes than those with grafts thicker than 130 µm. Busin et al. introduced the concept of ultrathin Descemet stripping automated endothelial keratoplasty (UT-DSAFEK) in which donor grafts thinner than 100 µm were transplanted. This subsequently led to many refinements to create ultrathin grafts. Two different clinical trials have demonstrated UT-DSAFEK resulted in the speedier recovery and a greater percentage of patients with improved final visual acuity compared with standard DSAFEK, while having similar surgical risks and complications. Recently, Cheung et al. reported a single pass technique to prepare donor grafts thinner than 50 µm. He named these remarkably thin grafts as nano thin Descemet stripping automated endothelial keratoplasty (NT-DSAFEK).

In 2006, Melles et al. introduced Descemet membrane endothelial keratoplasty (DMEK) in which only Descemet’s membrane and endothelial layer were transplanted after recipient descemeterohexis. Describing the first clinical result of this technique to an elderly male patient with Fuchs endothelial dystrophy, Melles et al. found the patient’s visual acuity to be 20/20 at 1 week after transplantation. Compared to DSEK, DMEK was a minimally invasive surgery with faster recovery times. Soon, DMEK became the most ideal form of surgery for endothelial dysfunction. However, the idiosyncrasy of Descemet membrane inherently increased the technical difficulty and complication rate. In an early series of evaluating reports, complications such as primary graft failure, graft detachment and dislocation, and donor tissue loss had a substantially higher rate of occurrence with DMEK than it did with DSAFEK. Additionally, loading the scroll into the injectors, unfolding and centering the tissue in the anterior chamber are all very difficult to manipulate in DMEK. These technical difficulties had initially halted DMEK from becoming as popular as DSAFEK. When DSAFEK surpassed PK and became the most commonly performed corneal transplantation in 2011, only 344 DMEK surgeries were documented in the eye bank statistic report that year. Nonetheless, the superior visual outcomes and faster recovery rate have been encouraging and more surgeons gradually switched to DMEK. Since 2011, the documented number of DMEK surgeries in the eye bank statistic report have doubled each year. The latest EBAA eye bank statistic report documented 6,459 DMEK surgeries in 2016 compared with 4,694 in 2015. Several recent meta-analyses comparing DSAFEK and DMEK have demonstrated that DMEK has faster recovery rate, better postoperative visual acuity, and less refractive error induction. The air rebubbling and repeat surgery rate are similar in both techniques after surpassing the learning curve in DMEK. In 2014, Lam
et al reported Hemi-Descemet membrane endothelial keratoplasty (Hemi-DMEK) with a purpose to increase donor tissue availability. The endothelial cell density decreased by 31-49% in their three patients at one month postoperative and another 7-24% between two to six months. However, all three patients received satisfactory visual outcomes. Earlier this year, Zygoura et al reported a six month outcome of Quarter-Descemet membrane endothelial keratoplasty (Quarter-DMEK) in twelve patients. They recorded 66% endothelial cell loss at six months postoperative but similar visual outcomes as conventional DMEK. Nonetheless, there are select patient populations such as those with phakic eye, aniridia, and previous glaucoma surgery where DSAEK, and especially UT-DSAEK, is presumed superior to DMEK.

Some patients experienced self-resolution of cornea edema without endothelial transplantation in surgeries associated with complications. This phenomenon can be partially explained by migration of existing endothelial cells. Since Fuchs endothelial dystrophy (FED) usually affects the central part of the cornea first, some surgeons stripped the central part of Descemet membrane and expected the peripheral endothelial cell to migrate to cover the denuded area without an endothelial transplant. The concept has various names such as Descemet stripping only (DSO), Descemetorhexis without endothelial keratoplasty (DWEK), Descemetorhexis without graft placement. The published case reports and case series had variable conclusions. Some patients achieved corneal clearing while others experienced constant corneal edema and poor visual acuity and final endothelial keratoplasty to improve vision. These inconsistent results may be caused by various corneal thickness, different endothelial cell migration capability associated with age, and the size of descemetorhexis. This technique may be considered in young patients with mild early central FED, but currently is not recommended as a routine alternative therapy.

While endothelial keratoplasty techniques were evolving rapidly by surgeons, other scientists have been trying to solve the same problem via a different approach. Attempts were made to inject the cultured endothelial cells into the anterior chamber. However, a major obstacle included properly adhering the cells to the posterior corneal surface and keeping them from transforming into a fibroelastic phenotype. Rho-kinase (ROCK) is the downstream effector of RhoA which is a small GTPase belonging to the Ras superfamily. RhoA/Rho-kinase pathway has multiple downstream effectors and is the regulating point of many cellular functions, such as cell migration, proliferation, cytoskeletal contraction, and apoptosis. Inspired by the study that ROCK inhibitor allowed the survival of dissociated embryonic stem cells, Okumura et al found the inhibition of Rho/Rho-kinase pathway improved monkey corneal endothelial cell adhesion and proliferation. Soon they carried the trials of cell injection therapy combined with the ROCK inhibitor in rabbit and monkey endotheliopathy models. They found that ROCK inhibition promoted both adhesion of injected endothelial cells to the posterior cornea and expression of endothelial functional proteins such as Na+/K+ -ATPase and ZO-1 in both animal models. After comprehensive examination by western blot and immunohistology, they proposed the theory in which ROCK inhibitor enhanced cell adhesion via blocking the phosphorylation of myosin light chain (MLC), reversing the downstream cascade, and keeping the endothelial cells in a hexagonal adherent state. Recently, they reported a 2-year clinical trial of 11 patients with bullous keratopathy injected with cultured human endothelial cells and ROCK inhibitor. Ten of the 11 patients achieved excellent visual acuity, corneal cell density, and central corneal thickness after two years of observation. Koizumi et al have also tried topical ROCK inhibitor as a potential treatment for early-stage endothelial diseases.

CONCLUSION

Without question, we have come a long way in the past 20 years. Since 1998, endothelial transplantation has changed dramatically from PK to DSAEK to DMEK. It has transcended all our expectations – becoming more minimally invasive with faster recovery times and improved visual outcomes. Two decades ago we would have never imagined our patients achieving near perfect visual acuity in a short span of time. It goes without saying the success of these procedures has benefited a countless number of patients over the years. Even more breathtaking, the future may involve patients receiving a simple injection, as the recent success of cultured cell injection with a ROCK inhibitor may start another era for treating endothelial diseases – a true testament to this constantly evolving field.

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Conflicts of Interest

There are no conflicts of interest.

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