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Graft Survival and Endothelial Outcomes in the New Era of Endothelial Keratoplasty

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Abstract

Corneal endothelial cells do not proliferate *in vivo* sufficiently to enable endothelial regeneration, and thus diseases of the corneal endothelium, which cause poor vision and discomfort, require treatment by transplantation of cadaveric donor corneal endothelial cells. The two major goals of any corneal transplant procedure are to restore vision and to promote longevity of the donor cornea by maintaining a healthy donor endothelial cell density. Over the last decade, the surgical treatment for endothelial disease has rapidly evolved toward endothelial keratoplasty, or selective tissue transplantation, and away from full-thickness penetrating keratoplasty (PK). While endothelial keratoplasty offers distinct advantages over PK in terms of visual outcomes and a smaller incision, the new surgical manipulations of the fragile donor tissue cause significant donor endothelial cell trauma. As a result, donor endothelial cell loss is much higher during the first month after Descemet stripping endothelial keratoplasty (DSEK) compared to after PK, and the primary (or more appropriately, iatrogenic) graft failure rate of 5% remains unacceptably high. Nevertheless, the rate of endothelial cell loss rapidly decreases beyond 6 months after DSEK, and thus endothelial cell loss at 5 years after DSEK appears to be lower than that at 5 years after PK. In the absence of primary (iatrogenic) graft failure, graft survival through 5 years after DSEK is similar to that after PK. Given the promising longer-term endothelial outcomes of DSEK, the quest for optimizing the visual outcomes has spurred interest in Descemet membrane endothelial keratoplasty (DMEK). While early results after DMEK suggest better visual outcomes than after DSEK, the technique needs to be simplified, and longer-term outcomes must show an advantage over DSEK with respect to vision, endothelial cell loss, and graft survival. DMEK also has a high rate of primary (iatrogenic) graft failure, and additional donor tissue wastage occurs when preparation of DMEK grafts is unsuccessful. This review discusses endothelial keratoplasty techniques and the associated endothelial outcomes.

Keywords

endothelial keratoplasty; penetrating keratoplasty; DSEK; DMEK; graft failure; endothelial cell density; endothelial cell loss; endothelium

Introduction

The corneal endothelium is a delicate monolayer of neural crest-derived cells that maintains corneal deturgescence and transparency. The endothelial cells do not proliferate to any significant extent *in vivo*, and therefore diseases of the corneal endothelium frequently result in morbidity by causing poor vision and discomfort. Our understanding of corneal

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endothelial cell biology has been dramatically advanced by Nancy Joyce, PhD, and her laboratory, not least with their efforts to determine how to stimulate proliferation of the senescent endothelial cells.

Despite the advances in the basic science mechanisms pertaining to endothelial cell biology and disease, the current treatment of endothelial disease remains surgical. In 2010, 42,000 corneal transplants were performed in the United States, and over half of these were for endothelial disease (EBAA, 2010). For decades, penetrating (full-thickness) keratoplasty (PK) was the only procedure for endothelial replacement. PK was first reported by Eduard Zirm in 1906 (Zirm, 1989), and subsequently refined by Ramon Castroviejo (Castroviejo, 1931, 1932a, 1932b). Since the late 1990s, the surgical treatment of endothelial disease has rapidly evolved, with the current treatment of choice being endothelial keratoplasty (EK); in 2010, 19,000 EK procedures were performed in the United States (EBAA, 2010). EK is an intraocular procedure in which posterior host corneal layers are replaced by posterior donor corneal layers to restore endothelial function. The advent of EK has heralded new techniques, new challenges, new complications, and new uncertainties for long-term outcomes.

This review discusses endothelial keratoplasty techniques and how they pertain to the integrity of the corneal endothelium. Outcomes with respect to endothelial cell loss and graft survival will be discussed primarily.

1. Keratoplasty for Endothelial Disease

Knowledge of the surgical techniques for EK is important for understanding the factors that cause endothelial cell loss. The EK era has generated new questions about the resilience of the corneal endothelium to surgical trauma and the resulting long-term effects on graft survival.

1.1 Penetrating keratoplasty

Penetrating keratoplasty was for years the only surgical treatment for corneal endothelial disease, but has now been superseded by EK (Patel, 2007). Nevertheless, PK will remain the treatment of choice or default for some eyes (Patel, 2011), and can be a successful vision restoring procedure for many patients (Patel et al., 2008; Price, FW et al., 1991). PK involves the replacement of full-thickness corneal host tissue with full-thickness corneal donor tissue (Figure 1). The donor tissue is cut by the surgeon with a trephine, resulting in inevitable endothelial cell loss at the cut edge; for 8 mm-diameter donor tissue trephinations, 6–9% of donor endothelial cells were damaged (Terry et al., 2009a; Terry et al., 2009b). The central host cornea is similarly excised with a circular trephine and the donor cornea is sutured to the host rim. Surgical manipulation of the donor tissue is minimal compared to EK techniques.

The PK technique is relatively simple compared to lamellar surgical techniques. Nevertheless, good visual outcomes require meticulous wound construction and tissue apposition, though ultimately a high spherocylindrical correction or rigid contact lens might be required to treat high or irregular astigmatism induced by the irregular shape of the anterior graft surface (Crawford et al., 1986; McLaren et al., 2009; Riddle et al., 1998). In addition, PK can be associated with ocular surface complications (Mannis et al., 1997; Meyer and Bobb, 1980; Thompson et al., 2003), suture-related infections (Christo et al., 2001; Forstot et al., 1975), and in rare cases, devastating expulsive hemorrhage intraoperatively or postoperatively (Price, FW et al., 1994; Purcell et al., 1982).

1.2 Posterior lamellar keratoplasty/deep lamellar endothelial keratoplasty

The modern era of EK began in the late 1990s when Melles described a posterior lamellar keratoplasty procedure to replace host endothelium, Descemet membrane, and posterior stroma, with donor tissue of a similar configuration (Figure 1) (Melles et al., 1998; Melles et al., 1999). With modifications, Terry introduced the procedure to the United States as deep lamellar endothelial keratoplasty (DLEK) (Terry and Ousley, 2001a). DLEK was slowly adopted because it required manual stromal lamellar dissection of the host and donor tissue, and was therefore technically challenging. Nevertheless, it was the first successful implementation of EK, and the procedure was advantageous over PK because there were no anterior corneal incisions or sutures, resulting in a predictable spherocylindrical correction for best vision and preventing suture-related complications, and it was performed through a smaller limbal incision (9 mm) providing better postoperative globe integrity in the event of postoperative trauma (Patel et al., 2008; Terry and Ousley, 2001b, 2005a). The anatomy of the virgin cornea was mimicked because the procedure typically provided a relatively continuous posterior corneal surface at the graft-host junction, similar to that after PK (Figure 1).

As experience with posterior lamellar keratoplasty/DLEK mounted, it became the first opportunity to transition EK from a large (9 mm) limbal incision to a smaller (5–6 mm) limbal incision, which was ideal for tectonic reasons (Melles et al., 2002a; Terry and Ousley, 2005b). However, reducing the size of the incision heralded new and significant surgical manipulations of the thin posterior donor lamella and therefore the donor endothelium (Patel, 2007; Terry et al., 2007). For placement into the eye, the donor tissue, which typically had a diameter of 8–9 mm, was folded, inserted through the small incision with forceps, unfolded in the anterior chamber, and positioned against the dissected recipient stromal bed. These additional manipulations, and the striae created in Descemet membrane by folding (Bahn et al., 1986), were, and still remain, factors associated with increased donor endothelial cell loss (see below).

1.3 Descemet stripping endothelial keratoplasty

Endothelial keratoplasty became more rapidly adopted with the realization that host Descemet membrane and endothelium could be easily stripped from the posterior stroma (Heindl et al., 2008; Melles et al., 2004), and that the donor lenticule could adhere to posterior stroma without dissecting a recipient bed (Figure 1) (Price, FW and Price, 2005, 2006). This eliminated the need for the technically challenging manual lamellar dissection of the host tissue, and stripping of Descemet membrane was facilitated in Fuchs dystrophy because the Descemet membrane is thicker than normal (Ahmed et al., 2010; Bourne et al., 1982). Shortly thereafter, manual lamellar stromal dissection of the donor tissue was also simplified by preparation of the tissue with semi-automated mechanical microkeratomes (Gorovoy, 2006; Price, FW and Price, 2006). As a result, Descemet stripping endothelial keratoplasty (DSEK) became the procedure of choice, and remains the most popular EK technique at this time. Rapid adoption of DSEK was enabled in part by the simpler technique compared to DLEK, and in part by eye banks preparing and distributing pre-cut donor lenticules (Price, MO et al., 2008). DSEK is an additive procedure because the host Descemet membrane and endothelium are replaced by donor stroma of variable thickness, Descemet membrane and endothelium (Ahmed et al., 2010) (Figure 1). The donor stroma acts as a carrier for the thin Descemet membrane and donor endothelium and thus aids handling of the tissue.

DSEK was initially performed through a small (5 mm) limbal incision (Price, FW and Price, 2005), and with minimal disruption of the anterior corneal surface, thus maintaining all the advantages of EK over PK. The small incision required surgical manipulation of the donor

tissue for insertion and positioning into the anterior chamber (Patel, 2007). In contrast to DLEK, in which the dissected recipient stromal bed facilitated adhesion of the donor tissue to the host, in DSEK, the donor tissue was apposed to the smooth posterior stromal surface by an intracameral air bubble. As a result, the earliest and most frequent (15% of cases (Lee, WB et al., 2009)) complication of DSEK was, and still is, donor tissue dislocation, which typically necessitates a further injection of intracameral air and repositioning of the donor tissue (Price, FW and Price, 2006).

The new surgical challenges associated with DSEK increased the risk of endothelial cell damage during the procedure. The most challenging aspect of DSEK, especially for novice surgeons, has been the insertion and positioning of the donor tissue. The original technique was forceps insertion of folded donor tissue into the anterior chamber (Price, FW and Price, 2005). With increasing popularity, a variety of insertion techniques were adopted, including pull-through and push-through methods (Balachandran et al., 2009; Macsai and Kara-Jose, 2007; Mehta et al., 2007; Vajpayee et al., 2006; Van Cleynebreugel et al., 2008). Incisions also became as small as 3 mm, which required either multiple folds or compression of the donor tissue for insertion (Price, MO et al., 2010). In human corneas *ex vivo*, a 5 mm limbal incision was associated with 18 to 20% endothelial cell damage, regardless of the method of insertion, whereas a 3 mm incision was associated with 30% cell loss (Terry et al., 2009a). Endothelial cell damage was highest (56% cell loss) when the donor tissue was compressed through a 3 mm incision without folding (Terry et al., 2009a). While forceps insertion of folded tissue remains acceptable, several insertion devices have been designed to help deliver the donor tissue into the anterior chamber (Busin et al., 2008; Khor et al., 2010). Intraocular lens cartridges have also been used to deliver the donor tissue with decreased endothelial cell loss compared to forceps insertion in human corneas *ex vivo* (Kuo et al., 2008).

Aside from surgical trauma related to the insertion method and incision size, other aspects of the DSEK technique contribute to cell damage. Intracameral air is associated with endothelial cell damage (Eiferman and Wilkins, 1981; Lee, DA et al., 1991; Tsubota et al., 1988) with as much as 10% cell loss (Hong et al., 2009). Laboratory simulations of donor tissue manipulation within the anterior chamber have not been reported, but simulation of anterior chamber collapse (i.e. iridolenticular touch) was associated with 55% cell loss (Lee, WB et al., 2007).

1.3 Descemet membrane endothelial keratoplasty

The additive nature of DSEK has been suggested to impair visual outcomes (Letko et al., 2011), and has thus spurred interest in selectively replacing host Descemet membrane and endothelium with donor Descemet membrane and endothelium alone to maintain normal corneal thickness and posterior curvature (Figure 1) (Dapena et al., 2009; Melles et al., 2002b; Melles et al., 2006). This procedure, called Descemet membrane endothelial keratoplasty (DMEK), is the latest form of EK offered at only a few centers worldwide. The adoption of DMEK has been slower than that of DSEK because of its increased technical difficulty, and, to date, the paucity of outcomes data that show a clear advantage over DSEK. The two new challenges that DMEK poses over DSEK are preparation of the donor tissue without wastage, and insertion, manipulation and adhesion of the thin membrane while minimizing damage to the donor endothelium.

Donor tissue preparation for DMEK has ranged from careful manual dissection (Laaser et al., 2011; Melles et al., 2006; Price, MO et al., 2009) to more complicated hybrid techniques (Busin et al., 2010; McCauley et al., 2009; Studeny et al., 2010). Manual dissection relies on the Descemet membrane forming a roll to aid with orientation of the endothelial side of the membrane, and subsequent insertion into the eye through an intraocular lens cartridge or

other device (Bachmann et al., 2010; Dapena et al., 2011; Price, MO et al., 2009). Although cell loss as low as 3.4% has been reported with manual dissection and insertion in human corneas *ex vivo* (Melles et al., 2002b), tearing of the donor Descemet membrane during preparation can render the tissue unusable for surgery (Melles et al., 2006). Difficult tissue preparation by experienced surgeons was reported for 17% of grafts, with 8% of grafts becoming unusable (Price, MO et al., 2009). To improve manipulation of the thin donor Descemet membrane, hybrid donor tissue preparation techniques are being developed in which peripheral donor stroma is retained for structural support while exposing the central Descemet membrane (Busin et al., 2010; McCauley et al., 2009; Studeny et al., 2010). In the hybrid technique, Descemet membrane is cleaved from the posterior stroma by injection of air, which can also result in perforation; this technique has been associated with 30% donor tissue wastage (Shah et al., 2009), although with more experience, the wastage rate decreases to 5% (Studeny et al., 2010).

Insertion and manipulation of the donor tissue in DMEK is more difficult than with DSEK, resulting in more frequent donor tissue dislocations, higher endothelial cell loss, and increased early graft failure (Ham et al., 2008; Laaser et al., 2011; Price, MO et al., 2009). Although the donor tissue can be stained with trypan blue to aid visualization and orientation (Bachmann et al., 2010; Melles et al., 2006), grafts are often oriented incorrectly with the endothelial cell surface apposed to recipient stroma (Ham et al., 2008). A “no-touch” technique has been described to minimize endothelial trauma (Dapena et al., 2011), and grafts with peripheral stromal support will be easier to manipulate, but there are no laboratory data assessing cell damage with these methods.

For DMEK to become widely adopted, the procedure will require minimal tissue wastage, donor tissue preparation by eye banks, a simple insertion technique, and few dislocations. In addition, the clinical outcomes of DMEK will need to supersede those of DSEK.

2. Endothelial Outcomes of Keratoplasty

The success of corneal transplantation has traditionally been assessed by graft survival, which is the time to graft failure (Coster and Williams, 2005). Endothelial cell loss has also been frequently reported, although cell loss might not always indicate overall loss of endothelial function (Lass et al., 2010). Visual outcomes were difficult to assess in the era of PK, but are gaining more importance as EK predominates (Patel, 2011). Keratoplasty outcomes should be interpreted with caution, especially when comparing different studies, because of variability in surgeon experience and techniques, and a lack of standardization for defining and measuring the outcomes. Furthermore, keratoplasty techniques have evolved so rapidly that sufficient data might not be available to rigorously determine some outcomes.

2.1 Endothelial cell loss

When comparing endothelial cell density (ECD) data between studies, it is important to know which endothelial analysis techniques were used and whether the microscopes were independently calibrated (McCarey et al., 2008). A few studies report microscope calibration for preoperative donor endothelial cell data for accurate comparison to postoperative data acquired with a different microscope (Bourne et al., 1994a; Cornea Donor Study Investigator Group et al., 2008b); however, most studies report the preoperative donor ECD as measured by the eye bank and assume an accurate calibration. In addition, because endothelial cell data after keratoplasty are derived from surviving grafts (failed grafts often cannot be measured), endothelial cell loss is typically underestimated.

2.1.1 Physiologic endothelial cell loss—Human corneal endothelial cells undergo little mitosis *in vivo*, although they do retain the ability to proliferate *in vitro* (Engelmann et al., 1988; Senoo and Joyce, 2000). As a result, endothelial cells are lost at a rate of 0.6% per year during adult life (Bourne et al., 1997), a rate that is low enough for most endothelia to function normally over a lifetime. Physiologic endothelial cell loss represents the death of stressed, senescent cells (Joyce et al., 2009), although the exact mechanism of cell death is not fully understood. The rate of endothelial cell loss increases after surgical procedures of the anterior segment, including after cataract surgery (Armitage et al., 2003; Bourne et al., 1994b).

2.1.2 Penetrating keratoplasty—During the first decade after PK, the annual rate of donor endothelial cell loss is 4–8% (Ing et al., 1998), but thereafter, the mean rate of cell loss approaches that of normal corneas, although individual grafts vary widely from the mean (Patel et al., 2010; Patel et al., 2005). In a large PK series by one surgeon (Bourne), endothelial cell loss from preoperative donor ECD was 34% at 1 year, 59% at 5 years, and 74% at 20 years (Figure 2) (Patel et al., 2010). Although this series included PKs for any recipient diagnosis, cell loss was similar between PK for keratoconus and for Fuchs dystrophy (Patel et al., 2010; Patel et al., 2005), and similar to other results (Sellevoll et al., 2009). The Specular Microscopy Ancillary Study to the Cornea Donor Study examined endothelial cell loss after PK for endothelial disease only and found a median cell loss of 70% at 5 years (Figure 2) (Cornea Donor Study Investigator Group et al., 2008b); this study has been extended to determine the effect of donor age on cell loss at 10 years.

Endothelial cell density in the early months after PK is predictive of late endothelial graft failure, whereas predicting late endothelial failure from preoperative ECD varies (Lass et al., 2010; Patel et al., 2010). This variable relationship indicates that endothelial cell function cannot be predicted simply by measuring ECD; 14% of clear grafts had an ECD <500 cells/mm² in the Specular Microscopy Ancillary Study (Lass et al., 2010).

2.1.3 Deep lamellar endothelial keratoplasty—In the largest reported series of DLEK, Terry et al. found that endothelial cell loss from preoperative ECD was 25% at 6 months, 26% at 1 year, and 37% at 2 years after surgery (Figure 2) (Terry et al., 2007). Cell loss at 2 years was higher with small incision (5 mm) DLEK than with large incision (9 mm) DLEK (Terry et al., 2007), and was the first clear indication that incision size affected cell loss; the effect of incision size in DLEK was also found in other studies (Fillmore et al., 2010; van Dooren et al., 2007). } At 5 years after DLEK in Terry's series, the large incision group had 60% cell loss from preoperative (Figure 2) (personal communication with Mark Terry on 4/10/11), no worse than cell loss after PK. However, in a smaller series of small incision DLEK, endothelial cell loss was 43% at 1 year, and 62% at 4 years (Mashor et al., 2010). The longest reported follow-up for DLEK is 10 years, with 79% endothelial cell loss in 15 surviving grafts (van Dijk et al., 2011).

2.1.4 Descemet stripping endothelial keratoplasty—There are several reports of endothelial cell changes after DSEK, but few reports beyond 12 months of follow-up. The American Academy of Ophthalmology recently published a comprehensive analysis of outcomes after DSEK, including endothelial cell loss (Lee, WB et al., 2009). In the larger series of DSEK, endothelial cell loss was high in the early postoperative period with 28% to 35% cell loss at 6 months, 31% to 36% at 12 months, and 31% to 41% cell loss at 24 months (Figure 2) (Price, MO and Price, 2008; Terry et al., 2011). Price et al. have reported the longest follow-up after DSEK with cell loss of 44% at 3 years and 54% at 5 years (Figure 2) (Price, MO et al., 2011). Thus, despite the high initial endothelial cell loss after DSEK compared to after PK, the rate of cell loss declines rapidly after 6 months (Price, MO et al.,

2011; Terry et al., 2011). In fact, at 5 years after DSEK, endothelial cell loss was lower than that at 5 years after PK in the Cornea Donor Study (Cornea Donor Study Investigator Group et al., 2008b; Price, MO et al., 2011). The reason for the apparent decline in cell loss after 6 months is unknown, and longer follow-up is needed to determine if this trend will persist. In a prospective study at Mayo Clinic, endothelial cell loss was highest in the first month after DSEK, with a slower rate of cell loss through 3 years (author's unpublished data), similar to that reported by Price et al (Price, MO et al., 2011).

Several factors increase endothelial cell loss after DSEK, including smaller incisions (Price, MO et al., 2010), longer incisions (Price, MO and Price, 2008), larger area of tissue compression by forceps (Price, MO and Price, 2008), and donor tissue dislocation (Price, MO and Price, 2008). Factors unassociated with endothelial cell loss include donor tissue storage time (Price, MO et al., 2011; Terry et al., 2011), graft diameter (Price, MO et al., 2011; Terry, 2009), preoperative ECD (Terry et al., 2008), manual versus microkeratome preparation of the donor tissue (Price, MO and Price, 2008), and the use of pre-cut versus surgeon-cut tissue (Price, MO et al., 2008). Early cell loss after DSEK using graft delivery devices, which do not require tissue folding or cause tissue compression, appeared to be lower in small, non-randomized series (Busin et al., 2008; Khor et al., 2010).

2.1.5 Descemet membrane endothelial keratoplasty—With DMEK in its infancy, there are only a few reports of early endothelial cell loss after this procedure. Price et al. found 30% cell loss at 3 months, and 32% at 6 months (Price, MO et al., 2009), whereas Laaser et al. found approximately 42% cell loss at 1, 3, and 6 months (Figure 2) (Laaser et al., 2011). The longest follow-up to date is for 7 eyes that had 34% cell loss at 2 years, although in the same but expanded series, cell loss was 36% at 1 year (Figure 2) (Ham et al., 2009b).

2.2 Graft Survival

The definition of graft survival, or more specifically, that of graft failure, varies between studies (Patel, 2011). Graft failure can be divided into primary failure, which is either early (primary donor failure) or late (late endothelial failure (Bell et al., 2000; Nishimura et al., 1999)), and secondary failure, in which there is a precipitating cause of failure, such as rejection or infection. Of note, primary donor failure after EK is better termed *iatrogenic graft failure* because most are caused by the surgical manipulation of donor tissue (Lee, WB et al., 2009).

2.2.1 Penetrating keratoplasty—The cumulative probability of developing graft failure and late endothelial failure after PK for any indication was 30% and 13%, respectively, at 20 years (Patel et al., 2010). Graft failure rates vary with the indication for PK, with grafts for keratoconus being less likely to fail from any cause or from late endothelial failure than grafts for endothelial disease (Patel et al., 2010; Patel et al., 2005). Similar results have been found in other large series (Thompson et al., 2003; Williams et al., 2008).

The 10-year failure rate of first PKs for Fuchs dystrophy varies from 10–20% (Ing et al., 1998; Pineros et al., 1996; Thompson et al., 2003), and is lower than that for pseudophakic or aphakic corneal edema (Ing et al., 1998; Thompson et al., 2003). The Cornea Donor Study, which examined graft survival after PK for endothelial disease, found that 14% of grafts failed by 5 years (Cornea Donor Study Investigator Group et al., 2008a), and the failure rate for Fuchs' dystrophy (7%) was lower than that for pseudophakic or aphakic corneal edema (Sugar et al., 2009). The primary donor and late endothelial failure rates in the Cornea Donor Study were <1% and approximately 4%, respectively, at 5 years (Cornea Donor Study Investigator Group et al., 2008a).

2.2.2 Deep lamellar endothelial keratoplasty—Graft survival data for DLEK are sparse and relatively short-term. Primary donor failure occurred in 1 to 8% of eyes (Fillmore et al., 2010; Mashor et al., 2010; Terry et al., 2007), higher than that after PK, and was more likely iatrogenic than attributable to the donor tissue. The rate of late endothelial failure was 1% at 2 years (Terry et al., 2007), 27% at 4 years (Mashor et al., 2010), and 14% at 10 years, (van Dijk et al., 2011) in three separate studies.

2.2.3 Descemet stripping endothelial keratoplasty—Primary or iatrogenic graft failure is much higher after DSEK than after PK; the reported rates vary (Lee, WB et al., 2009), although higher rates are likely to be associated with surgeon inexperience. In the larger DSEK series, and thus those by surgeons with the most experience, Terry had no primary graft failures (Terry et al., 2008), and Price reported a 3.5% failure rate (Price, FW and Price, 2006); most other studies report the rate to be less than 10% with an average of 5% (Lee, WB et al., 2009).

The rate of late endothelial failure after DSEK is difficult to ascertain because there are few reports with more than 2 years of follow-up. At five years, Price et al. found that 2.4% of grafts failed because of late endothelial failure and concluded that the overall graft failure rate for DSEK was similar to that after PK in the Cornea Donor Study (Price, MO et al., 2011). Although the rate of late endothelial failure after DSEK is similar to that after PK and poor visual outcomes might become a more common cause of graft failure (Letko et al., 2011; Price, MO et al., 2011), Price et al. did not include the primary/iatrogenic graft failures in their 5-year analysis (Price, MO et al., 2011), and these were in fact the most common cause of graft failure through 5 years (Price, FW and Price, 2006).

2.2.4 Descemet membrane endothelial keratoplasty—The primary or iatrogenic graft failure rate in initial reports of DMEK is 6 to 8% (Ham et al., 2009a; Price, MO et al., 2009), and is in addition to 8% donor tissue wastage during preparation (Price, MO et al., 2009). Longer follow-up is required to determine late endothelial failure rates.

3. Visual Outcomes

The initial experience and results of DSEK have provided optimism for long-term graft survival and for the potential of restoring normal vision. The major advantages of EK over PK for vision are better uncorrected visual acuity and a predictable postoperative refractive error (Chen et al., 2008; Patel et al., 2009; Price, FW and Price, 2005). Although PK can provide a similar rate of visual recovery as DSEK (Patel et al., 2009), visual recovery is considered to be quicker, and quality of vision better, after DSEK than after PK. Nevertheless, quality of vision is not restored to normal (Seery et al., 2011a), and attention has focused on the variable thickness of the donor tissue in DSEK (Ahmed et al., 2010) and to mismatch in curvature of the graft and host that might increase optical aberrations (Seery et al., 2011b). This has spurred the current interest in DMEK, which offers the potential for improved visual outcomes (Price, MO et al., 2009). Nevertheless, the success of DMEK will also require that endothelial cell loss and graft survival to be similar to or better than those after DSEK. In addition, changes in the anterior cornea as a result of chronic endothelial dysfunction might also affect visual outcomes in some cases, irrespective of the method of endothelial replacement (Hecker et al., 2011; Patel et al., 2009).

4. Future Prospects for Treating Endothelial Disease

Future treatments for endothelial disease would ideally avoid the need for surgery, and might include pharmacologic agents to stimulate endothelial cell proliferation (Joyce and Harris, 2010; Okumura et al., 2011; Okumura et al., 2009) or function (Hatou et al., 2010),

or therapies to slow or halt disease progression. Until such novel therapies become available, keratoplasty will remain the mainstay of treatment, and efforts should continue to improve keratoplasty techniques and outcomes. Most important at the present time are methods to protect the donor endothelium during EK to reduce the high rate of primary/iatrogenic graft failure (Fuchsluger et al., 2011). In addition, a better understanding of the mechanisms of chronic endothelial cell loss and senescence (Joyce et al., 2011) might help improve graft longevity. Transplantation of cultured corneal endothelial cells should be further developed to help expand the donor pool (Hitani et al., 2008; Koizumi et al., 2007; Mimura et al., 2007; Patel et al., 2009). While the prospects for future treatment of endothelial disease are vast, they all require continued understanding of endothelial cell biology in normal and transplanted corneas, and improved knowledge of the mechanisms of disease, and we are indebted to Nancy Joyce for setting this precedent.

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Figure 1. Schematic representation of different keratoplasty techniques for endothelial disease
Top Left, In penetrating keratoplasty, the full-thickness host cornea is replaced by a full-thickness donor cornea to provide donor endothelial cells (yellow). Sutures are required to secure the donor tissue to the host. *Top Right*, In deep lamellar endothelial keratoplasty, the posterior host corneal stroma, Descemet membrane and endothelium are excised through a large or small limbal incision and replaced with donor tissue consisting of similar layers. This provides donor endothelial cells (yellow) without corneal incisions or sutures, but introduces an irregular, manually dissected lamellar interface between the donor tissue and host corneas. *Bottom Left*, In Descemet stripping endothelial keratoplasty, host Descemet membrane and endothelium are stripped from the host posterior corneal stroma, and replaced with donor tissue consisting of posterior stroma, Descemet membrane and endothelium. This provides donor endothelial cells (yellow) without an anterior corneal incision or corneal sutures. Because the donor tissue is usually prepared with a mechanical microkeratome, and the posterior stromal surface is not disrupted, the lamellar interface between donor tissue and host is regular, but the procedure adds a variable thickness of stromal tissue. *Bottom Right*, In Descemet membrane endothelial keratoplasty, host Descemet membrane and endothelium are stripped from the host posterior corneal stroma, and selectively replaced with donor Descemet membrane and endothelium (yellow). This anatomically mimics the native cornea without requiring an anterior corneal incision, but manipulation of the thin, delicate donor membrane can be technically challenging.

Figure 2. Comparison of donor endothelial cell loss by keratoplasty technique

Donor endothelial cell loss in the early postoperative period is higher after endothelial keratoplasty than after penetrating keratoplasty (PK). At 2 years, cell loss from preoperative is comparable between PK, deep lamellar endothelial keratoplasty (DLEK) with a 9 mm incision, and Descemet stripping endothelial keratoplasty (DSEK). At 5 years, cell loss after DSEK appears to be lower than that after PK. Only data from larger series were included for clarity, and thus data for Descemet membrane endothelial keratoplasty (DMEK) are only shown through 12 months. When endothelial cell densities were not reported, the data were estimated from the reported endothelial cell loss. The primary surgeon for each series is indicated; CDS, Cornea Donor Study.