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Evolving Techniques in Corneal Transplantation

Grace E. Boynton and **Maria A. Woodward**

Department of Ophthalmology and Visual Sciences, University of Michigan Medical School, Kellogg Eye Center, 1000 Wall St., Ann Arbor, MI 48105, USA

Maria A. Woodward: mariawoo@med.umich.edu

Abstract

Corneal transplantation is one of the most common types of human transplant surgery. By removing a scarred or damaged host cornea and replacing it with a clear and healthy donor transplant, this procedure helps to restore vision in a variety of corneal diseases. The traditional technique for corneal transplantation, penetrating keratoplasty (PKP), involves transplantation of all corneal layers. Over the past decade though, there has been a trend away from PKP as surgeons have developed partial thickness transplant procedures, such as deep anterior lamellar keratoplasty and Descemet stripping automated endothelial keratoplasty. These partial thickness transplant procedures selectively replace diseased host corneal tissue, while conserving healthy and functioning tissue. This review describes current surgical techniques in the field of corneal transplantation, with special emphasis on indications for transplantation and postoperative outcomes.

Keywords

Corneal transplantation; Descemet stripping endothelial keratoplasty; Penetrating keratoplasty; Descemet membrane endothelial keratoplasty; Deep anterior lamellar keratoplasty

Introduction

The cornea is a clear protective tissue barrier that covers the front of the eye. By virtue of its transparency and domed shape, it also allows the passage of incoming light rays and focuses them on the retina. The average adult cornea is 550 μm and consists of five layers: the corneal epithelium, Bowman's layer, the corneal stroma, Descemet membrane, and the corneal endothelium. The outermost layer of the cornea is the epithelium, which blocks the entry of foreign materials and absorbs oxygen and nutrients from tears. Directly below the epithelium is Bowman's layer, a clear layer of modified stroma. Beneath Bowman's layer is the stromal layer, which contributes the bulk of the cornea's thickness, and is composed of

Correspondence to: Maria A. Woodward, mariawoo@med.umich.edu.

Compliance with Ethics Guidelines

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regularly-arranged collagen fibrils and keratocytes. Descemet membrane is a basement membrane that lies between the stroma and the corneal endothelium. The corneal endothelium is the innermost layer of the cornea, and is only one cell layer thick. It has the important function of pumping excess fluid out of the stroma to maintain corneal transparency.

The transparency of the cornea depends on its relative state of dehydration, its avascularity, and the uniformity of its structure. Because the cornea contains no blood vessels, it depends on the aqueous humor, tears, and the limbal blood supply for nutrition. Disease and injury can cause scarring, opacification, and corneal irregularity with subsequent distortion of incoming light rays and reduced vision. In some circumstances, vision can be restored through corneal transplantation, where a diseased or scarred host cornea is replaced with a transparent and healthy transplant. In fact, this procedure is frequently indicated and corneal transplantation is one of the most common types of human transplant surgery. In 2013, 48,229 corneal transplants were performed in the US [1], compared to 28,953 solid organ transplantations which occurred that same year (including kidney, pancreas, liver, intestine, heart, and lung) [2]. Although corneal transplantation has high success rates, the procedure is not without risk. Intraoperatively, poor graft centration, suprachoroidal hemorrhage, infection, and damage to surrounding ocular structures can occur. Postoperative risks include transplant wound dehiscence, infection, graft rejection, graft failure, disease recurrence, and severe astigmatism.

Corneal transplantation is indicated in a variety of settings and can be performed in several ways depending on the location of pathology in the host cornea (Fig. 1). Historically, penetrating keratoplasty (PKP) was the mainstay surgery for corneal transplantation. In this procedure, the central portion (approximately two-thirds) of the diseased host cornea is removed entirely and replaced with a donor graft that includes all five layers of the cornea. Newer targeted transplant surgeries have been developed, including deep anterior lamellar keratoplasty (DALK), Descemet stripping automated endothelial keratoplasty (DSAEK), and Descemet membrane endothelial keratoplasty (DMEK). These procedures allow for selective replacement of diseased host corneal tissue, with conservation of healthy and functioning portions of the cornea. In DALK, the host Descemet membrane and endothelium are retained, and the donor graft contains only the anterior cornea, with a varying amount of corneal stroma. Conversely, for endothelial keratoplasty (EK), the posterior portion of the cornea is transplanted and the anterior portion of the cornea is retained. In one version of EK, DSAEK, the transplanted graft includes the corneal endothelium, Descemet membrane, and a thin layer of corneal stroma. In another version of EK, DMEK, the transplanted graft consists only of Descemet membrane and the corneal endothelium. In recent years, EK has become the most commonly performed corneal transplant surgery in the US [1], reflecting the fact that the majority of diseases of the cornea are of the corneal endothelium.

In this review, we describe the rapidly evolving field of corneal transplantation, with special emphasis on indications for transplantation, current surgical techniques, and postoperative outcomes.

Penetrating Keratoplasty

The first successful PKP was performed by Eduard Zirm in 1905, and PKP remained the mainstay for corneal transplantation throughout the remainder of the twentieth century. Over the last decade though, there has been a trend away from PKP, in favor of partial-thickness transplantation procedures. In 2005, 42,063 grafts were used in PKP surgeries in the US, and in 2013, only 20,954 grafts were used for this purpose in the United States [1]. Common indications for PKP include keratoconus, graft replacement after prior graft failure, full-thickness corneal scars, Fuchs' endothelial dystrophy, pseudophakic or aphakic bullous keratopathy, infection, and trauma (Table 1). The basic surgical technique for PKP involves first marking the visual axis of the host cornea. The host cornea is then trephinated, and their diseased central cornea is excised. In its place, a full-thickness corneal button is transplanted from donor corneal-scleral tissue and sutured into place. After suturing, the transplant is checked to ensure a tight wound seal between the donor and recipient tissue. Femtosecond lasers can also be used, in a technique known as femotosecond laser-assisted keratoplasty (FLAK), to prepare both donor and recipient corneas [3, 4].

One advantage of PKP is that the full thickness tissue does not create any tissue interfaces in the visual axis and is thus optically clear. This offers a visual benefit over partial thickness transplants. However, there are some increased intraoperative and postoperative risks associated with PKP, intraoperative hemorrhage (because the ocular contents are "exposed" to the air for a period of time during the procedure), postoperative wound leak, and endophthalmitis. Postoperative vision is frequently limited by astigmatism and anisometropia which needs to be managed by selective suture removal over the first postoperative year. Additionally, globe stability is reduced postoperatively, and patients are susceptible to higher rates of globe rupture at the incision site from blunt trauma even years after surgery.

Several large studies have analyzed graft survival following PKP, and preoperative and postoperative risk factors impacting graft survival [5, 6, 7•]. A study examining 18,686 PKP grafts in the Australian Corneal Graft Registry found that the probability of graft survival was 87 % at 1 year, 73 % at 5 years, 60 % at 10 years, and 46 % at 15 years [5]. The Cornea Donor Study, which prospectively followed 1,090 patients undergoing PKP, found a 75 % cumulative graft success rate at 10-years within their study cohort [7•]. A third retrospective review of 3,992 eyes found that first time grafts had survival rates of 90 and 82 % at 5 and 10 years, respectively [6]. However, survival rates for regrafts were much lower, with 53 % at 5 years and 41 % at 10 years.

Endothelial decompensation is one of the most common causes for graft failure, occurring in 24 % [5]–45 % [7•] of failed grafts. Functioning corneal endothelium is essential for graft survival, and there is a steady loss of endothelial cells following PKP. Studies have demonstrated 61 % [8]–67 % [9] mean endothelial cell loss by the 10th postoperative year. Graft rejection is another frequent cause of graft failure, occurring in 27 % [6]–34 % [5, 7•] of grafts. Less common causes of graft failure include uncorrectable refractive error, infection, and ocular surface complications.

A variety of preoperative and postoperative risk factors influence graft survival [10••]. Multiple studies have demonstrated that graft survival varies with indication for PKP. The 10-year follow-up data from one study showed 89 % survival for keratoconus, 73 % survival for Fuchs' dystrophy, 66 % for nonherpetic scar, 59 % for herpetic eye disease, 42 % survival for bullous keratopathy, and 37 % survival for re-grafts [5]. There are also higher incidences of graft rejection associated with certain preoperative diagnoses. For example, in the Cornea Donor Study, the 10-year cumulative probability of a rejection event among patients with Fuchs' dystrophy was 13 %, but individuals with pseudophakic or aphakic corneal edema had a 21 % probability of experiencing a rejection event [10••]. Donor age does not appear to be an important determinant of graft survival except for at the very extremes of age [5, 7•]. Postoperative rejection episodes [5, 10••], preoperative history of glaucoma [10••], and larger graft size [5] are all factors associated with a higher risk of graft failure.

Deep Anterior Lamellar Keratoplasty (DALK)

In DALK, the host epithelium and stroma are removed, ideally to the level of Descemet membrane. The transplanted donor graft consists of donor epithelium, Bowman's membrane, and the corneal stroma. DALK is an alternative to PKP when the host endothelium is functional and pathology is limited to the anterior cornea. DALK is frequently performed for keratoconus and partial thickness corneal scars (Table 1).

Several variations in technique are used to excise the host anterior cornea in DALK. Traditionally, the anterior corneal layers are manually dissected until the deep stroma or Descemet membrane is reached. In recent years, alternative dissection techniques to separate the stroma from Descemet membrane have gained popularity, including injection of balanced salt solution [11] or viscoelastic [12] into the posterior stroma. Pneumatic dissection, used in Anwar and Teichmann's "Big Bubble technique", is a commonly performed. In this technique, air is injected into the cornea to create a dissection plane between the stroma and Descemet membrane [13].

One major advantage of DALK compared to PKP is that, with retention of the host endothelium and Descemet membrane, there are lower postoperative rates of endothelial cell loss and lower rates of rejection. In a study of 214 patients who underwent DALK for keratoconus, mean endothelial cell loss was 22 % at 8 years [14], roughly a third of that recorded 10 years after PKP [8, 9]. There is also a lower incidence of graft rejection following DALK, compared to PKP [15]. Furthermore, post-operative rejection events in DALK patients are more likely to be reversible than in PKP patients [15]. One concern specific to DALK is that it can create an irregular stroma-to-stroma interface if not all of the host stroma is removed. While interface irregularities could potentially limit postoperative vision following DALK, PKP and DALK patients have comparable average postoperative visual acuity. For keratoconus patients, 78 % [16]–87 % [17] of those who undergo DALK and 73 % [18]–86 % [19] of those who undergo PKP achieve 20/40 best corrected visual acuity or better. Astigmatism after DALK is also comparable to that after PKP [20]. Intraoperative complications specific to DALK include microperforations of Descemet membrane, and macroperforations of Descemet membrane that necessitate conversion from

DALK to PKP. Studies report 1 % [21]–4 % [17] rates of conversion to PKP; however, it is likely higher in clinical practice.

Descemet Stripping Automated Endothelial Keratoplasty (DSAEK)

DSAEK is the most commonly performed keratoplasty in the US, with 49.0 % of corneas distributed for this purpose in 2013 in the United States [1]. It is an appropriate therapy for endothelial dysfunction. Indications for DSAEK include Fuchs' corneal dystrophy, pseudophakic or aphakic bullous keratopathy, failed prior keratoplasty, endothelial decompensation secondary to prior surgery or trauma, posterior polymorphous dystrophy, and iridocorneal endothelial syndrome (Table 1).

In DSAEK, the diseased host corneal endothelium and Descemet membrane are removed and replaced with a donor graft consisting of corneal endothelium, Descemet membrane, and a variable amount of posterior stroma. A variety of techniques are used in preparation of the donor graft. First, a donor corneoscleral rim is mounted on an artificial anterior chamber (ACC), and hand dissection or an automated microkeratome is used to cut a posterior corneal button [22]. Although there is a lower risk of graft perforation with automated preparation compared to manual dissection, microkeratome-prepared DSAEK corneas are still frequently non-uniform, non-concentric, and non-circular [23]. In an effort to increase graft uniformity, femto-second preparation of DSAEK tissues has been explored. However, femto-prepared tissues have had greater irregularity of the posterior surface and increased thickness irregularity when compared to microkeratome-prepared tissues [24, 25]. The preparation of ultrathin DSAEK lenticules of ≤100 μm thickness is another emerging area of interest. Double-pass microkeratome techniques have been used to create thinner grafts [26], however, this has resulted in increased perforation rates [27] and increased endothelial damage [28] in some studies. In the final step of donor graft preparation, the tissue is trephinated so that it fits the area of removed tissue in the host eye.

Following graft preparation, a variety of insertion techniques can be used to place the donor graft in the host anterior chamber and adhering it to the posterior cornea. The original strategies for graft insertion involved folding the donor lenticule and using a set of non-compressing forceps to push it through a small corneal or scleral incision. A number of alternative insertion techniques were subsequently developed to minimize endothelial cell damage that occurred with graft manipulation and folding. Alternative insertion techniques include pulling an unfolded donor lenticule over a modified Sheets glide [29], pulling a donor lenticule over a funneled glide [30], and closed-chamber pulling-injection techniques [31]. Several instruments have also been developed to aid with lenticule insertion into the host anterior chamber [32, 33]. Following tissue insertion into the anterior chamber, the corneal incision or scleral tunnel is closed. The lenticule is positioned and centered in the anterior chamber, and an air bubble is delivered into the anterior chamber so that its borders extend beyond the edges of the lenticule. The patient lies supine, and the air bubble holds the donor graft in place to the host posterior stroma until the donor endothelial pump function works to hold the tissue in place within the first few minutes to hours.

One major advantage of DSAEK compared to PK is reduced wound size and thus reduced induced astigmatism. An analysis of post-EK outcomes found that, on average, DSAEK

induces only .11 D of astigmatism [34]. Visual recovery also occurs more quickly in DSAEK compared to PKP. In one study comparing DSAEK to PKP, 70 % of DSAEK and 25 % of PKP patients obtained 20/40 acuity or better by 12 months. It was not until 2–3 three years after surgery that PKP patients obtained their final refractive result, at which point 55 %had 20/40 acuity or better [35]. A systemic review of studies reporting postoperative DSAEK outcomes found that average vision varied from 20/34 to 20/66 at a range of 3–21 months following DSAEK [34].

As DSAEK is a newer technique than PKP, there is less information about long-term graft survival following DSAEK than with PKP. However, several studies have reported 3-year DSAEK graft survival rates, and found them to be non-inferior to graft survival following PKP. One retrospective cohort study reported 87 % DSAEK graft survival and 85 % PKP graft survival at 3 years [36]. A second prospective trial reported 96 % DSAEK graft survival and 96 % PKP graft survival at 3 years for Fuchs' dystrophy cases, and 86 % DSAEK survival and 84 % PKP graft survival at 3 years for non-Fuchs' cases [37].

The most common complications following DSAEK include graft dislocation, endothelial rejection, primary graft failure, and iatrogenic glaucoma. Graft dislocation is the most frequent complication, and it tends to occur in the early postoperative period. Dislocation rates range widely with technique and surgeon experience, with studies reporting dislocation rates of 1.5 % [38]–85 % [39]. Primary graft failure is also a major cause of graft failure, and occurs in 0 % [40]–18 % [41] of grafts. Both endothelial cell failure and trauma or excessive manipulation of the graft can induce primary graft failure. Endothelial cell loss is accelerated following DSAEK, and a systemic review reported an average of 37 % endothelial cell loss by 6 months postoperative [34]. Cell loss continues after the immediate postoperative period, but at a slower rate, such that, by 5 years, one study found a loss rate of 53 % [42].

Descemet Membrane Endothelial Keratoplasty (DMEK)

In DMEK, the transplanted lenticule consists solely of donor Descemet membrane and the corneal endothelium. As DMEK grafts contain no stroma, an advantage of this procedure is that it does not produce a stroma-to-stroma interface. Like DSAEK, DMEK is a therapeutic option for patients with endothelial dysfunction (Table 1). Although challenges associated with preparing and handing delicate DMEK grafts have limited its widespread use, the procedure is growing in popularity. From 2012 to 2013, there was a 103.5 % increase in the total number of DMEK cases performed in the US [1].

A variety of techniques are used to harvest DMEK donor grafts. In manual peeling, described by Melles et al., the donor corneoscleral rim is immersed in BSS and a single set of non-toothed forceps are used to peel the DM [43–45]. Other instrumentation used to manually peel the DM includes using two sets of forceps [46, 47] or curvilinear forceps [48]. An alternative technique to manual peeling is submerged corneas using backgrounds away (SCUBA), which was described by Giebel and Price [49, 50]. In SCUBA, the cornea is submerged in Optisol or BSS during harvesting to mitigate surface tension, and to allow the DM to settle onto the stroma. Pneumatic dissection is another alternative to manual peeling of the DM [51–53]. As in DALK, pneumatic dissection in DMEK involves injecting air into

the cornea to create a dissection plane between the donor stroma and DM. Another DMEK graft preparation method was recently described by Muraine et al. [54•]. In their technique, a subtotal superficial trephination is performed on a donor cornea to create a flap, and then BSS is then injected underneath the flap to detach the DM. After stripping the donor DM, it is trephinated. The donor graft will naturally form into a roll, with the endothelial side facing outwards.

The host is prepared by stripping away the diseased DM and endothelium [55]. Several instruments are used to insert DMEK grafts into the host cornea, including glass pipettes [56] and intraocular lens injection cartridges [46, 54•]. Once the rolled donor graft has been inserted into the host anterior chamber, it needs to be unfolded. One technique is to inject a small air bubble or BSS into the center of a rolled graft to unfold it. Another technique is to introduce an air bubble on top of the graft and move it to unfold the graft by pressing a cannula against the outer corneal surface [57]. Yoeruek et al. described an unfolding technique where digital pressure is applied at the equatorial plane, and the cornea is tapped on the outside surface to facilitate unfolding of the graft [58]. Once the graft is completed unfolded, is centered in the anterior chamber by gently applanating the outer cornea surface. Once the graft is centered, the anterior chamber is filled with air or gas [59] to achieve good apposition between the DMEK graft and host posterior stroma.

One of the main advantages of DMEK over DSAEK is that it results in better visual acuity. Tourtas et al. completed a retrospective case series comparing visual outcomes in patients who had undergone DMEK and DSAEK, and found the DMEK patients had significantly better visual acuity than DSAEK patients at 3 and 6 months postoperative [60]. In their series, 50 % of DMEK patients and 6 % of DSAEK patients achieved a visual acuity of 20/25 or better after 6 months postoperative. In another prospective study of patients undergoing DMEK, 74 % achieved a corrected visual acuity of 20/25 or better by 6 months postoperative [61]. In a comparative case series of 15 patients who underwent DMEK in one eye and DSAEK in the contralateral eye, 85 % of interviewed patients said that their DMEK-treated eye had better quality of vision than their DSAEK-treated eye [62•].

A second advantage of DMEK is that there is a reduced risk of graft rejection compared to DSAEK and PKP. Reported rates of rejection following DMEK include 0.7 % [63], 0.8 % [57], and 5.1 % [64]. Anshu et al. completed a retrospective case series of patients who underwent DMEK, DSAEK, and PKP to evaluate the comparative risks of postoperative rejection episodes in each group [63]. They found that, within the first 2 postoperative years, DMEK eyes had a 15-fold lower risk of experiencing a rejection episode than DSAEK eyes and a 20-fold lower risk compared to PKP eyes.

One drawback of DMEK is the challenge of manipulating the thin grafts. Surgeons report that, with improvements in techniques and instrumentation, loss rates can be greatly reduced [64]. Furthermore, an increasing number of eye banks are preparing DMEK grafts, which will facilitate the ease of the procedure for many surgeons. Graft detachment is the most common complication following DMEK and requires additional injection of air into the anterior chamber. Rebubbling rates vary with experience and technique. While early reports

cited rebubbling rates up to 82 % [60], more recent studies have reported rebubbling rates as low as 3 % [65].

Conclusion

Significant advances in the field of corneal transplantation have been made in the past century, and in especially in recent decades. Transplantation of all corneal layers, through PKP, is becoming less frequent as surgeons are growing to favor procedures that selectively replace diseased tissue, such as DSAEK and DMEK. With growing surgeon experience and modifications in technique, these procedures are yielding improved visual acuity, fewer complications, and faster visual recovery times. With a limited supply of donor corneas available in many regions of the world, the field of corneal transplantation is rapidly evolving to optimize clinical outcomes and protect the vision of transplant recipients.

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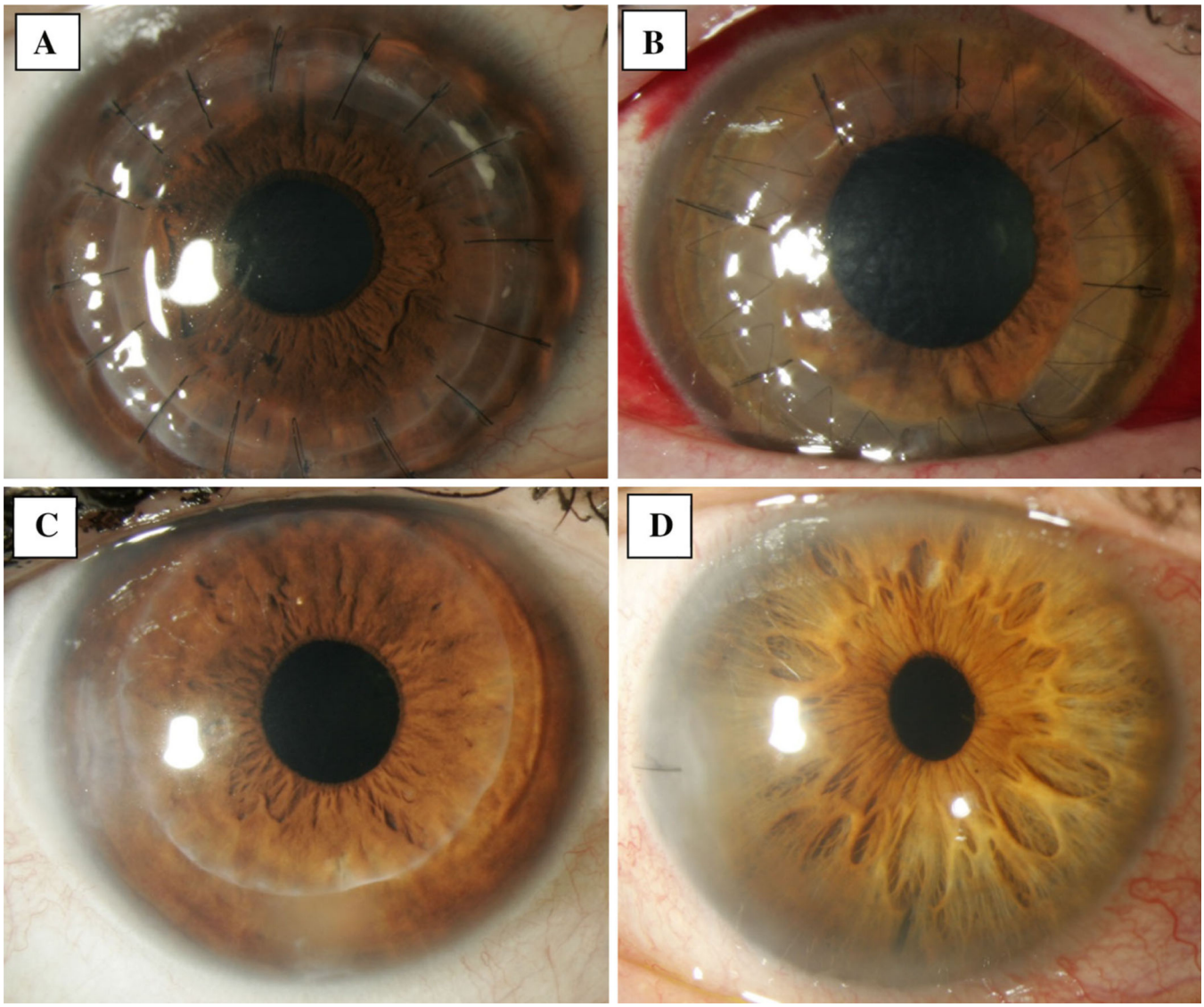

Fig. 1.

Slit lamp photographs following **a** penetrating keratoplasty, **b** deep anterior lamellar keratoplasty, **c** Descemet stripping automated keratoplasty, and **d** descemet membrane endothelial keratoplasty

Table 1

Overview of corneal transplantation procedures: techniques, indications, and complications

	PKP	DALK	DSAEK	DMEK
Surgical technique	All layers of the diseased host cornea removed	Diseased host epithelium and stroma removed	Diseased host endothelium and Descemet membrane removed	Diseased host endothelium and Descemet membrane removed
	Transplant of full-thickness donor graft	Transplant of donor cornea epithelium, Bowman's membrane, & corneal stroma	Transplant of donor endothelium, Descemet membrane, & stroma	Transplant of donor endothelium and Descemet membrane
Common indications for selected technique	Full-thickness scar, bullous keratopathy, keratoconus, graft failure	Keratoconus, stromal scar, hereditary stromal dystrophies	Fuchs' dystrophy, bullous keratopathy, graft failure	Fuchs' dystrophy, bullous keratopathy, graft failure
Major complications	Graft rejection, graft failure, hemorrhage, infection, astigmatism, suture complications	Graft rejection, intraoperative Descemet membrane tear, astigmatism	Graft detachment, graft failure, graft rejection	Graft detachment, graft failure

PKP penetrating keratoplasty, *DALK* deep anterior lamellar keratoplasty, *DSAEK* Descemet stripping automated endothelial keratoplasty, *DMEK* Descemet membrane endothelial keratoplasty