Corneal transplantation for keratoconus
Hornhinntransplantasjon ved keratokonus

Sven Jonuscheit, Michael J. Doughty
Vision Sciences, Department of Life Sciences, Glasgow Caledonian University, Cowcaddens Road, Glasgow, G4 0BA, UK

Abstract
This review discusses current techniques of corneal transplantation for moderate to advanced keratoconus. The aim of this article is to provide primary eye care practitioners with an overview of two current corneal transplantation modalities, namely penetrating and deep anterior lamellar keratoplasty. The main surgical techniques, the outcome of the procedures, common complications and the prognosis will be reviewed. Results from ongoing studies at a corneal transplant centre in Glasgow, Scotland will be discussed.

Sammandrag

Received September 12, 2012, accepted February 13, 2013
Key words: Cornea, corneal transplantation, keratoconus, penetrating keratoplasty, deep anterior lamellar keratoplasty, endothelium
Correspondence: sven.jonuscheit@gcu.ac.uk

Introduction
Keratoconus is traditionally considered to be a localised, non-inflammatory, progressive and bilateral but often asymmetric degeneration of the cornea. The onset is usually in the second decade of life, and while progression is variable, keratoconus frequently stabilises in the fourth decade. The incidence of keratoconus is about 1 in 2,000 and the prevalence around 55 per 100,000 (Castroviejo, 1948; Rabinowitz, 1998).

In many countries keratoconus is initially managed in primary eye care settings, e.g. in optometric practice, especially in the early stages of the disease. Advanced cases are more likely to be managed in either specialised optometric practices or secondary eye care settings such as ophthalmology departments of hospitals.

The treatment of early keratoconus usually consists of conservative non-invasive correction of the refractive error and astigmatism by fitting spectacles (if the astigmatism is relatively regular). Cases with more advanced keratoconus and with associated substantial and irregular astigmatism will be fitted with various types of special hydrogel and gas permeable contact lenses, which constitute the main treatment modality. Special types of lenses with a dual soft-gas permeable design can also be used, although these are less frequently fitted (Lim & Vogt, 2002).

In advanced keratoconus, visual acuity can often no longer be corrected satisfactorily with optical devices. Some patients experience contact lens intolerance, with a subsequent negative impact on daily life, e.g. at the workplace. These patients may still benefit from contact lenses optically, but are not able to wear their lenses for the required period, e.g. for eight or more hours per day. If visual acuity deteriorates so that it is unsatisfactory or if the contact lens tolerance and daily wearing time fall below an acceptable threshold, then corneal surgery can be considered. Initial surgical options include corneal collagen cross-linking with riboflavin and UV (Snibson, 2010), intra-stromal corneal segments (Pinero & Alio, 2010) and ultimately corneal transplantation. The focus of this review are the two most common corneal transplantation modes, penetrating keratoplasty (PK) and deep anterior lamellar keratoplasty (DALK).

Clinical signs and symptoms
Keratoconus is characterised by a variety of clinical signs, many of which can be detected using equipment readily available in optometric practice. Classical signs of keratoconus include a cone-shaped cornea with an inferiorly decentred apex, central and/or paracentral stromal thinning, high, and in advanced stages, irregular astigmatism, reduction in visual acuity, iron deposits around the cone at the level of the epithelial basement membrane (Fleischer’s ring) and so-called stress lines in the posterior stroma near the level of Descemet’s membrane (Vogt’s striae). In advanced keratoconus, Munson’s sign, a depression of the lower lid margin upon downward gaze, may be observed. These signs can occur independently or in conjunction with other signs. While several clinical signs may be present, patient symptoms can vary and will depend on the stage of the keratoconus. Common symptoms include reduced spectacle- or contact lens-corrected visual acuity, ocular irritation and contact lens intolerance, although some patients, especially those with early stage keratoconus, are likely to be asymptomatic (Rabinowitz, 1998).

Aetiology of keratoconus
Even though keratoconus has been a focus of eye research for at least a century, its aetiology is not fully understood. Keratoconus often occurs in isolation, but has been reported to be associated with a range of other conditions including atopy, Down syndrome, Leber’s congenital amaurosis and eye rubbing (Rabinowitz, 1998). Some authors have referred to keratoconus as a “multifactorial” disease and genetic causes have been investigated (Nielsen, Hjortdal, Pihlmann, & Corydon, 2012). Despite intensive research on the causes for keratoconus, the true aetiology “…still remains a mystery” (Nielsen et al., 2012). Nevertheless, keratoconus is a common indication for keratoplastic surgery (Edwards et al., 2002; Rabinowitz, 1998; Rahman, Carley, Hillarby, Brahma, & Tullo, 2009; Ting et al., 2012). In recent studies the non-inflammatory nature of keratoconus has been re-considered with assessments of the tear film of patients with keratoconus showing that various inflammatory mediators or markers are present in higher concentration than in non-keratoconic eyes (Balasubramanian, Mohan, Pye, & Willcox, 2012; Lema & Duran, 2005). Such inflammatory markers include various types of cytokines such as Interleukin-6. Cytokines have a role in initiating and regulating inflammatory responses of the ocular surface. Increased levels of such inflammatory markers suggest that the idea of keratoconus being non-inflammatory in nature can no longer be maintained, but that keratoconus may at least in part have an inflammatory component to its aetiology. A “cascade hypothesis” has also been proposed, which suggests that the development and progression of keratoconus could be linked to oxidative stress (Cristina Kenney & Brown, 2003).
Corneal hydrops
When the keratoconus has progressed to an advanced stage, patients may experience a rupture or break of Descemet’s membrane. Such a break in Descemet’s membrane causes a breakdown of the barrier function of the endothelium across the posterior corneal surface. The result is leakage of aqueous into the corneal stroma, which causes an increase in corneal hydration with associated corneal stromal swelling (oedema), reduction of corneal transparency and ultimately deterioration of visual acuity (Suzuki & Minarick, 2009). This phenomenon has been termed hydrops and can lead to a permanent reduction in vision, caused primarily by persistent intra-corneal scarring that develops as Descemet’s membrane slowly regenerates. If the scarring is located centrally, i.e. on the visual axis, optical correction with spectacles or contact lenses is likely to be insufficient. Clinical studies commonly report on corneal hydrops in the form of case reports or case series, making a reliable estimate of the incidence difficult.

Keratoconus as an indication for keratoplasty
Keratoconus is a common indication for keratoplasty (Edwards et al., 2002; Rabinowitz, 1998; Ting et al., 2012). In patients with contact lens intolerance, permanent central corneal scarring (e.g. after hydrops) and associated impaired quality of vision, surgical treatment of keratoconus is the only option to improve or restore visual function. The surgical treatment for advanced keratoconus is often the only option to restore vision to usable (functional) levels. Because optometrists are frequently involved in managing keratoconus, it is, from an optometric perspective, essential to recognise the best point in time when a keratoconus patient should be referred to an ophthalmic surgeon for assessment of their suitability for keratoplasty. To streamline the referral process, good communication with the local ophthalmology department is implicit. Similar to other surgical interventions, optometrists need to consider the age of the patient and the level of impairment, as well as the impact of the keratoconus stage on the patient’s quality of life. Since keratoconus frequently affects younger populations with a relatively long life expectancy, all factors need to be taken into account, because younger patients may require more than one graft during their lifetime (Kelly, Williams, & Coster, 2011).

Number of keratoplasty procedures performed
The number of keratoplasties performed in a country is likely to vary and may depend on factors such as the type of the health care system in a particular country. In England, between 1400 and 2000 transplants were carried out per year in the early 1990s (Keenan et al., 2010). Another recent report indicated that approximately 2500 corneal grafts are registered with the National Health Service (NHS) Blood and Transplant register in the whole of the UK annually (Jones, Armitage, Ayliffe, & Jones, 2013). In the Western region of Scotland (with Glasgow as the main surgical centre) 921 keratoplasties were performed between 2001 and 2010 and keratoconus was the leading indication for keratoplasty (29% of all keratoplasties) (Ting et al., 2012). In Sweden, 448 keratoplasty procedures were performed in 1999 (Fagerholm, Claesson, & Stenevi, 2002). Corneal transplant data are being collated by the Swedish Cornea Transplant Register, which was established in 1997 (Claesson, Armitage, Fagerholm, & Stenevi, 2002).

As part of an ongoing clinical study at the Tennent Institute of Ophthalmology, Gartnavel General Hospital in Glasgow, Scotland, UK, one hundred functioning corneal grafts were assessed, 76% of which were performed for keratoconus. This number represents approximately the number carried out in Glasgow in one calendar year (Jonuscheit, Doughty, & Ramaesh, 2012). In other specialized centres in the UK the mean number of grafts performed at each centre is approximately 38 cases per annum and this includes keratoconus as well as a range of other indications (Koay, Lee, & Figueiredo, 2005).

Penetrating keratoplasty
As reviewed by Reinhart et al., PK was first successfully used in a human eye over a century ago in 1905 by German ophthalmologist Eduard Zirm (Reinhart et al., 2011; Zirm, 1906). Zirm used PK to treat a case of chemical injury of a male patient, who had suffered a bilateral chemical burn with chalk/calcium carbonate as the offending agent. Following Zirm’s report, surgical techniques and postoperative management advanced and PK subsequently became the most commonly used form of corneal transplantation in the second half of the 20th century. PK probably still is the most popular technique (Tan et al., 2012) and is considered a highly successful procedure (Tan, Anshu, & Mehta, 2009). The PK-technique involves the replacement of all five corneal layers (epithelium, Bowman’s membrane, stroma, Descemet’s membrane and endothelium) (Tan et al., 2012). PK is a versatile procedure and can be used in conditions that affect any layer of the cornea, including the endothelium. For example, PK can be used to treat penetrating eye injuries or eyes with deep stromal scarring. Surgeons also tend to be more familiar with the technique than with more technically challenging transplantation modes (Reinhart et al., 2011). In a patient with keratoconus, which affects primarily the anterior corneal layers, PK is a surgical option, but the replacement of all corneal layers is not necessarily required as the replacement of Descemet’s membrane and the endothelium are not essential, except in some cases with previous hydrops. However, even if a replacement of the endothelium is not needed, PK may produce a potentially better visual outcome than DALK, in part because in PK there is no lamellar interface between the residual corneal tissue of the patient and the donor tissue that could result in optical distortions (Tan et al., 2012).

Deep anterior lamellar keratoplasty
Lamellar (partial) replacement of corneal layers has been used for more than one hundred years (von Hippe1, 1888). Modern forms of DALK involve replacing parts of the diseased cornea with donor tissue, but rather than transplanting a full thickness corneal button Descemet’s membrane and the endothelium are left in situ. For keratoconic corneas, this means specifically the epithelial and stromal layers are being removed from the recipient cornea, whereas the two innermost layers, Descemet’s membrane and the endothelium, remain in place. In contrast to PK, a feature of DALK is an interface between the posterior layers of the host (recipient) cornea and the transplanted donor tissue. Following several decades during which PK was the primary keratoplasty technique, the interest in lamellar keratoplasty procedures was revived a little over ten years ago by reports of new surgical techniques that offered a greater chance...
of achieving a deeper dissection with a more regular interface between donor and recipient cornea with improved visual outcomes (Anwar & Teichmann, 2002; Melles et al., 1999; Melles, Remeijer, Geerards, & Beekhuis, 2000). One of the techniques that has received significant attention and which has probably been the most publicised of the different lamellar techniques is DALK, and a recent review provides details on the variants of the technique (Reinhart et al., 2011). In brief, the technique involves removal of most or all of the central stroma, but leaves Descemet’s membrane and the corneal endothelium intact. Because DALK avoids the complete opening of the ocular surface that is a characteristic of PK it provides a theoretical safety margin by avoiding complications such as microbial endophthalmitis, expulsive choroidal haemorrhage, flat anterior chamber from wound leaks and primary donor graft endothelial failure (Reinhart et al., 2011). Numerous approaches have been proposed and tried to separate and remove the stromal layers including manual dissection with a trephine and a blade (Sugita & Kondo, 1997) and/or injection of saline (Sugita & Kondo, 1997), air (Anwar & Teichmann, 2002) or a viscoelastic (Melles et al., 1999; Melles et al., 2000) into the stroma. The so-called “big bubble” technique by Anwar is currently the most commonly used technique at Gartnavel General Hospital in Glasgow. The big bubble technique involves injection of air into the stroma to create an intra-stromal bubble that allows for easier separation of the stromal tissue. A primary aim of all of these approaches is to remove the stroma and to bare Descemet’s membrane in order to create a smooth interface for the donor cornea button. In recipient corneas with residual stromal tissue, the interface between donor and recipient cornea will be less regular and this may impact on the visual outcome of the procedure (Al-Torbak et al., 2006; Reinhart et al., 2011).

Advantages of DALK over PK are generally considered to include the avoidance of immunological rejection of the corneal endothelium, a less severe loss of endothelial cells, the extraocular nature of the procedure and less postoperative topical corticosteroid use (Reinhart et al., 2011; Tan et al., 2012). Avoiding the risk of immunological endothelial rejection is highly desirable as the occurrence of rejection has been shown to be associated with a higher risk for graft failure of PK (Anshu, Lim, Htoon, & Tan, 2011; Kelly et al., 2011) and avoidance of postoperative risk factors such as endothelial rejection may lead to improved long-term graft survival (S. V. Patel, 2011).

PK is, however, still the most common modality of keratoplasty (S. V. Patel, 2011) and advancements in drug technology and the development of topical corticosteroid eye drops have contributed to an increase in PK survival rates. One reason for the popularity of PK is the potential for problems with the donor-recipient interface in DALK. DALK is technically more demanding than PK and an irregular interface between donor and recipient cornea at the level of deep stroma can be associated with a poorer visual outcome of DALK (Tan et al., 2009).

An emerging development is the use of a femtosecond laser for corneal transplantation. The femtosecond laser can be used to dissect the stroma in DALK and to create incisions for corneal trephinations in PK (Baradaran-Rafi & Eslami, 2012).

Prognosis and cost-effectiveness
PK carried out for keratoconus generally have a good short-term (L. Lim, Pesudovs, & Coster, 2000) and long-term prognosis with 80% of grafts still being clear at on average 27 years after surgery (Jensen, Hjortdal, & Ehlers, 2010). Jensen and colleagues also note that patients who received a PK for keratoconus have a high chance of having visual acuity of better than 0.5 (Snellen decimal, equivalent to Snellen 6/12 or 0.3 logMAR) at 20 years after surgery. PK for keratoconus also has a better prognosis than grafts for other indications, but it is likely that younger recipients of a PK will require one or more repeated keratoplasties during their lifetime (Kelly et al., 2011). Long-term outcome and survival data of DALK are not yet readily available, but it has been reported that DALK results in fewer postoperative complications than PK (Han, Mehta, Por, Htoon, & Tan, 2009). Five-year postoperative data and long-term predicted survival rates also show promising results with the median predicted graft survival of DALKs for indications not affecting the endothelium (including keratoconus) being 49 years (Borderie et al., 2012). Evidence for these long lifetimes of DALK that were predicted by statistical models is, however, not yet available.

PK is a cost-effective transplantation procedure (Roe, Lass, Brown, & Brown, 2008) and while lamellar techniques such as DALK are increasingly used for the treatment of keratoconus (Borderie et al., 2009; Reinhart et al., 2011), few reports are available that document the cost-effectiveness of the procedure. A recent study from the US indicated a favourable cost-effectiveness ratio of DALK and the authors recommended DALK as a first line treatment for keratoconus (Koo, Finkelstein, Tan, & Mehta, 2011). An economic evaluation of DALK for various indications not affecting the endothelium, which was carried out in the Netherlands, concluded that DALK procedures are both more costly and more effective than PK in the long term, but that cost effectiveness over a 12 month (or longer) period remains unclear (van den Biggelaar et al., 2011).

Eye banking in Scandinavian and other European countries
Keratoplasty requires human tissue, usually from organ donors, to be readily available. In order to survive, corneal transplants depend on a functional (viable) endothelial cell layer and preservation of the endothelium is the main purpose of corneal storage (Armitage, 2011). Across Europe 62 eye banks are in operation (Armitage, 2011) that collect, prepare, store and distribute donor corneal tissue to transplant centres, i.e. hospitals. In the UK, eye banks are located in London, Manchester and Bristol. In Scandinavian countries, there are eye banks in Århus (Denmark), Oslo and Trondheim (Norway), as well as in Linköping, Lund, Mölndal, Örebro and Stockholm (Sweden) (European Eye Bank Association, http://europeaneyebanks.com; accessed 29 May 2012). Various methods are used for corneal storage including hypothermic storage at 2-8 degrees Celsius, organ culture (storage in a culture medium such as Eagle’s minimum essential medium (MEM)) and the nowadays rarely used cryopreservation (Armitage, 2011). The majority of corneas in Europe are stored in organ culture for up to four weeks, but this can be extended to up to seven weeks. Suitability for keratoplasty is assessed at the eye bank, commonly by light microscopy and assessment of the endothelial cell density (ECD). At the Bristol eye bank, a minimum ECD of 2200 cells/mm² is required for corneal tissue to be suitable for transplantation (Armitage, 2011). About 70% of European eye banks apply a minimum level of 2,000 cells/mm², whereas the remaining 30% of eye banks have minimum ranging from 2,100 to 2500 cells/mm² (Armitage, 2011).

Visual outcome
A great number of studies have reported the outcome of keratoplasty carried out in Australia, Denmark, France, Italy, Singapore, the UK and the US (Borderie et al., 2012; Fontana, Parente, & Tassinari, 2007; Han et al., 2009; Jensen et al., 2010; Jones et al., 2009; Larkin, Mumford, & Jones, 2011; L. Lim et al., 2000; S. V. Patel, Hodge, & Bourne, 2005; Sarnicola, Toro, Gentile, & Hanush, 2010; Smedja et al., 2012; Vail et al., 1997). Postoperative visual acuity is one common outcome measure. The visual outcome of selected studies is shown in Table 1. The studies differ substantially in the way visual acuity is reported, in follow-up
operative events can increase the probability for graft rejection (Claesson & Armitage, 2009). Data from Glasgow show that a greater number of postoperative complications, such as suture-related inflammation, epithelial defects resulting in corneal infection, uveitis, and conjunctivitis, may increase the risk for corneal graft rejection (Borderie et al., 2009; Claesson & Armitage, 2009; Jones et al., 2009; Koay et al., 2005; Panda et al., 2007; Sellami et al., 2007; Tham & Abbott, 2002; Vail et al., 1997; Wagoner et al., 2009; Williams, Kelly, Lowe, & Coster, 2010). The risk for recipients of PK to develop rejection has been predicted to be 23% at 15 years postoperatively (S. V. Patel et al., 2005).

The reasons for this difference between the studies are not clear, but it could be speculated that socio-economic factors (relatively high prevalence of deprivation in the Glasgow area) and differences in diet and possibly alcohol consumption may have an effect. A number of studies have reported on the occurrence of and risk factors for corneal graft rejection (Borderie et al., 2009; Coster & Williams, 2005; Epstein, de Castro, Laibson, Cohen, & Rapuano, 2006; Inoue, Amano, Oshika, & Tsuru, 2001; Koay et al., 2005; Panda et al., 2007; S. V. Patel et al., 2005; Reinhart et al., 2011; Sellami et al., 2007; Tham & Abbott, 2002; Vail et al., 1997; Williams et al., 2010). Risk factors include inflammatory events such as suture-related inflammation, epithelial defects resulting in corneal infection, uveitis, and conjunctivitis. Various studies show that predicting factors for graft rejection include repeated keratoplasty (i.e. that the same patients received a subsequent graft), graft size, significant corneal vascularisation, previous graft rejection episodes and previous herpetic eye disease (Epstein et al., 2006; Koay et al., 2005; Vail et al., 1997). Other events appear to be independent in the risk for rejection and these include surgical suturing techniques, loose or broken sutures during the postoperative phase and the percentage of sutures remaining in the transplant (Epstein et al., 2006).

Even though several preoperative, surgical and graft recipient factors have been identified as predictors for graft rejection, relatively little has been reported on the overall effect of other postoperative complications on the risk for corneal graft rejection. A recent study suggests that in patients who were treated with keratoplasty in both eyes, the occurrence of a rejection episode in one eye increases the risk for rejection in the second eye (Williams et al., 2010). A recent report by the American Academy of Ophthalmology has confirmed that DALKs have no inherent risk of developing rejection episodes to occur. This finding was confirmed by multiple logistic regression controlling for confounding effects of variables such as subject age, time since the procedure, endothelial cell count, and type of graft.

### Graft rejection

Graft rejection is a significant postoperative complication of penetrating corneal transplantation and has been described as a major cause or risk factor for graft failure (Anshu et al., 2011; Coster & Williams, 2005; Panda et al., 2007; H. Y. Patel et al., 2011; Tham & Abbott, 2002; Wagoner et al., 2009; Williams, Kelly, Lowe, & Coster, 2010). The risk for recipients of PK to develop rejection has been predicted to be 23% at 15 years postoperatively (S. V. Patel et al., 2005). Results of studies carried out in Glasgow show that despite excellent long-term visual outcomes, the overall probability for rejection in patients treated with PK was around 32% at 15 years after the procedure was performed. The reasons for this difference between the studies are not clear, but it could be speculated that socio-economic factors (relatively high prevalence of deprivation in the Glasgow area) and differences in diet and possibly alcohol consumption may have an effect.

A number of studies have reported on the occurrence of and risk factors for corneal graft rejection (Borderie et al., 2009; Coster & Williams, 2005; Epstein, de Castro, Laibson, Cohen, & Rapuano, 2006; Inoue, Amano, Oshika, & Tsuru, 2001; Koay et al., 2005; Panda et al., 2007; S. V. Patel et al., 2005; Reinhart et al., 2011; Sellami et al., 2007; Tham & Abbott, 2002; Vail et al., 1997; Williams et al., 2010). Risk factors include inflammatory events such as suture-related inflammation, epithelial defects resulting in corneal infection, uveitis, and conjunctivitis. Various studies show that predicting factors for graft rejection include repeated keratoplasty (i.e., that the same patients received a subsequent graft), graft size, significant corneal vascularisation, previous graft rejection episodes and previous herpetic eye disease (Epstein et al., 2006; Koay et al., 2005; Vail et al., 1997). Other events appear to be independent in the risk for rejection and these include surgical suturing techniques, loose or broken sutures during the postoperative phase and the percentage of sutures remaining in the transplant (Epstein et al., 2006).

### Visual outcome after keratoplasty in selected studies

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Country</th>
<th>N</th>
<th>Graft type</th>
<th>Follow-up time (months)</th>
<th>Visual acuity (LogMAR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lim, 2000</td>
<td>Australia</td>
<td>93</td>
<td>PK</td>
<td>46 (mean)²</td>
<td>0.24</td>
</tr>
<tr>
<td>Fontana, 2007</td>
<td>Italy</td>
<td>78</td>
<td>DALK</td>
<td>24</td>
<td>0.10 (approx.)¹</td>
</tr>
<tr>
<td>Han, 2009</td>
<td>Singapore</td>
<td>14</td>
<td>DALK</td>
<td>24</td>
<td>0.12 (SD 0.15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11</td>
<td>DALK</td>
<td>24</td>
<td>0.23 (SD 0.17)</td>
</tr>
<tr>
<td>Jones, 2009</td>
<td>UK</td>
<td>1136</td>
<td>PK</td>
<td>24</td>
<td>0.24 (SD 0.25)</td>
</tr>
<tr>
<td>Jensen, 2010</td>
<td>Denmark</td>
<td>61</td>
<td>PK</td>
<td>324 (mean)²</td>
<td>0.24 (SD 0.40)</td>
</tr>
<tr>
<td>Sarnicola, 2010</td>
<td>Italy</td>
<td>94</td>
<td>pdDALK</td>
<td>30 (mean)²</td>
<td>0.10 (approx.)¹</td>
</tr>
<tr>
<td>Larkin, 2011</td>
<td>UK</td>
<td>572</td>
<td>PK</td>
<td>24</td>
<td>0.3 (median)</td>
</tr>
<tr>
<td>Smadja, 2012</td>
<td>France</td>
<td>32</td>
<td>DALK</td>
<td>12</td>
<td>0.10 (approx.)¹</td>
</tr>
</tbody>
</table>

¹Visual acuity values were given in decimal notation in the paper and converted to LogMAR for easier comparison.
²Subjects were assessed at different follow-up intervals.
³Variations of the DALK procedure were compared. For full details please refer to the original publication.

### Postoperative complications

Various postoperative complications can occur after keratoplasty including corticosteroid-induced increase in IOP, epithelial defects, trauma, infective keratitis, suture-related problems, recurrence of the original disease and wound leaks (Anshu et al., 2011; Awan et al., 2010; Borderie et al., 2009; Claesson & Armitage, 2009; Jones et al., 2009; Koay et al., 2005; Panda, Vanathi, Kumar, Dash, & Priya, 2007; Reinhart et al., 2011; Wagoner, Ba-Abbad, Al-Mohaimeed, Al-Swailem, & Zimmerman, 2009). Complications have been shown to affect the postoperative visual outcome as well as the survival of corneal transplants (Claesson & Armitage, 2009; Vail et al., 1997; Wagoner et al., 2009). Data from Glasgow show that a greater number of postoperative events can increase the probability for graft rejection.
following devastating endothelial rejection, because the endothelium of the recipient is retained (Reinhart et al., 2011). However, DALKs may still experience epithelial or stromal rejection, which can be considered as being less severe and which are not usually associated with graft failure. In addition, the rate of rejection following DALK appears to be low with no cases of rejection reported for a cohort of 25 patients who were treated with DALK and followed for up to 24 months (Han et al., 2009). No rejection episodes were noted within the first year after surgery in a cohort of 42 patients who received a DALK for keratoconus (Smadja et al., 2012). For PK, the probability for remaining rejection-free was 95% during the first year after surgery (Jonuscheit, Doughty, & Ramaesh, 2013).

The corneal endothelium after keratoplasty

Corneal transparency of healthy eyes as well as after surgery is, in part, dependent upon endothelial function (Edelhauser, 2006). The status of the endothelium can be assessed by making estimates of the shape, the size and the number of cells present (i.e. endothelial cell density, ECD) (Doughty, Muller, & Zaman, 2000; McCoy, Edelhauser, & Lynn, 2008; Oblak, Doughty, & Oblak, 2002). Various microscopes are available for the acquisition of endothelial micrographs with specular and confocal microscopy being typically used for in-vivo measurements (Doughty, 1989; Doughty, Jonuscheit, & Button, 2011; Jonuscheit, Doughty, & Ramaesh, 2011; Jonuscheit et al., 2012; McCoy et al., 2008). After PK, the number of endothelial cells declines at an increased (exponential) rate of 4.2% per year between the fifth and tenth year after the procedure, as compared to the normal cell loss of about 0.6% per year that occurs in non-operated healthy eyes (Bourne, 2001). A bi-exponential cell loss function has been suggested with a dramatic cell loss initially and a return to a loss rate similar to that in non-operated eyes after several years (Armitage, Dick, & Bourne, 2003). During the PK procedure, the endothelium can be compromised by surgical trauma, e.g. through preparation of the donor button and the recipient bed or the suturing procedure.

Following DALK, data from Glasgow show that there can be a disturbance of the endothelium during the early postoperative period, which is more obvious following PK, but also noticeable after DALK (Figure 1). However, differences in the cells are less prominent at about five years after surgery (Figure 2) (Jonuscheit et al., 2013). Endothelial cell density is commonly higher following DALK than after PK with mean cell counts of 2215 vs. 1019 cells/mm² (Jonuscheit et al., 2011) and similar values have been reported by other groups for patients treated with DALK (Fontana et al., 2007).

However, following penetrating keratoplasty the endothelial cell density can vary widely with reported values ranging from 320 to 1980 cells/mm² up to 33 years after surgery (Abbott, Fine, & Guillet, 1983; Basak, 2004; Bourne, 2001; Inoue, Kimura, Amano, Oshika, & Tsuru, 2002; Jonuscheit et al., 2011, 2012; Kus, Seitz, Langenbucher, & Naumann, 1999; Matsuda & Bourne, 1985). Relatively low endothelial cell counts have been suggested as a precursor to corneal decompensation, but whether there is a definable limit remains doubtful (Kus et al., 1999), as even grafts with fairly low cell counts (e.g. 600-700 cells/mm²) often remain clear and functional (Basak, 2004; Jensen et al., 2010; Kus et al., 1999). One suggested lower limit of endothelial cells required to maintain endothelial function and corneal clarity was 700 cells/mm² (Basak, 2004), but keratoplasties with fewer cells are often functioning and clear. It is not yet well established how variable the cell densities might be after DALK. Studies are currently underway at Glasgow to establish whether there are substantial differences in cell densities following DALK and to identify possible reasons for this.

Summary and Conclusions

Full-thickness and partial thickness (lamellar) corneal transplantation procedures are available to surgeons considering keratoplasty for a keratoconus patient. Both transplantation modalities offer a good prognosis for keratoconus patients with visual impairment that is not correctable with traditional optical methods such as contact lenses or spectacles. Optometrists need to be aware of the options available and be able to decide on the appropriate point in time for referral to secondary care for consideration of surgical treatment modalities.

Acknowledgements

The authors thank Dr Kanna Ramaesh, Tennent Institute of Ophthalmology, for useful discussions. The authors are also grateful for the support by The Royal College of Surgeons (Edinburgh) for their grant support to Dr Kanna Ramaesh of the ongoing studies at the Tennent Institute of Ophthalmology.

References


Figure 1: Representative post-operative endothelial confocal image obtained 6 months after DALK (A) and 6 months after PK (B). Scale bar = 50 micrometers; from Jonuscheit et al., *Clin Exp Optom* 2013; with permission.

Figure 2: Representative post-operative endothelial confocal images 5 years after DALK (A) and 5 years after PK (B). Scale bar = 50 micrometers; from Jonuscheit et al., *Clin Exp Optom* 2013; with permission.


Lim, N., & Vogt, U. (2002). Characteristics and functional outcomes of 130 patients with keratoconus attending a specialist contact lens clinic. Eye (London), 16(1), 54-59. doi: 10.1038/sj.eye.6700061


