Corneal transplantation for keratoconus
Hornhinnetransplantasjon ved keratokonus

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Abstract

This review discusses current techniques of corneal transplanta-
tion for moderate to advanced keratoconus. The aim of this arti-
cle is to provide primary eye care practitioners with an overview
of two current corneal transplantation modalities, namely pene-
trating and deep anterior lamellar keratoplasty. The main surgi-
cal techniques, the outcome of the procedures, common compli-
cations and the prognosis will be reviewed. Results from ongo-
ing studies at a corneal transplant centre in Glasgow, Scotland
will be discussed.

Sammendrag

Denne oversiktsartikkelen tar for seg alminnelig ubredte
metoder for ornhinnetransplantasjon ved moderat og
langtkommet keratokonus. Målet med denne artikkelen er
å gi førstelinje helsepersonell innen øyehelsetjenste oversikt
over to alminnelig utbredte metoder for hornhinnetransplan-
tasjon, penetrerende og fremre lamellær keratoplastikk. De
mest vanlige operasjonsmetodene, resultater av prosedyrene,
vanlige komplikasjoner og prognose blir diskutert. Resultater
fra pågående studier ved et senter for hornhinnetransplantasjon
i Glasgow, Skottland, blir lagt frem og diskutert.

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 ker-
atoconus 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 pri-
mary 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 sec-
ondary eye care settings such as ophthalmology departments of
hospitals.

The treatment of early keratoconus usually consists of conser-
vative non-invasive correction of the refractive error and astig-
matism by fitting spectacles (if the astigmatism is relatively reg-
ular). Cases with more advanced keratoconus and with associ-
ated 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 be-
low an acceptable threshold, then corneal surgery can be con-
sidered. 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 com-
mon 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 advancenced
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 pos-
terior stroma near the level of Descemet's membrane (Vogt's
striae). In advanced keratoconus, Munson's sign, a depres-
sion of the lower lid margin upon downward gaze, may be ob-
served. 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 (Rabi-
nowitz, 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. Kera-
toconus 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 rub-
bing (Rabinowitz, 1998). Some authors have referred to kerato-
conus 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 kerato-
plasty (Edwards et al., 2002; Rabinowitz, 1998; Rahman, Car-
ley, Hillarby, Brahma, & Tullo, 2009; Ting et al., 2012). In re-
cent studies the non-inflammatory nature of keratoconus has
been re-considered with assessments of the tear film of pa-
tients with keratoconus showing that various inflammatory me-
diators or markers are present in higher concentration than in
non-keratoconic eyes (Balasubramanian, Mohan, Pye, & Will-
cox, 2012; Lema & Duran, 2005). Such inflammatory markers
include various types of cytokines such as Interleukin-6. Cy-
tokines have a role in initiating and regulating inflammatory re-
sponses of the ocular surface. Increased levels of such inflam-
matory 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 compo-
nent to its aetiology. A "cascade hypothesis" has also been pro-
posed, 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 tissue, which causes an increase in corneal hydration with associated corneal stromal swelling (oedema), reduction of corneal transparency and ultimately deterioration of visual acuity (Suzuki & Minarcik, 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 of 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, Larkin, & Kaye, 2009). In 2010 and 2011, 3565 corneal transplants were preformed in the UK (Tan, Dart, Holland, & Kinoshita, 2012). 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 a 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 58 cases per annum and this includes keratoconus as well as a range of other indications (Koay, Lee, & Figueiredo, 2005).

Keratoplasty techniques for keratoconus

Two surgical techniques are commonly used in the management of moderate to advanced keratoconus, full thickness corneal transplantation, also known as penetrating keratoplasty (PK) and deep anterior lamellar keratoplasty (DALK). Both techniques offer advantages and surgeons are faced with a decision as to which mode is the most suitable for a particular patient. From an optometrist's perspective it seems paramount to be informed about current treatment options so that keratoconus patients who are intolerant to contact lenses or have uncorrectable visual impairment through keratoconus can be informed in detail prior to being referred to an ophthalmic surgeon.

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 Hippel, 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 Descement'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-Rafii & Eslani, 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/mm^2 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/mm^2, whereas the remaining 30% of eye banks have minima ranging from 2,100 to 2500 cells/mm^2 (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, & Hannush, 2010; Smadja 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

Table 1: Visual outcome after keratoplasty in selected studies.

First author, year	Country	Nº of eyes	Graft type	Follow-up time (months)	Visual acuity (LogMar)
Lim, 2000	Australia	93	PK	46 (mean)[2]	0.24
Fontana, 2007	Italy	78	DALK	24	0.10 (approx.)[1]
Han, 2009	Singapore	100	PK	24	0.25 [SD 0.27]
		14	DALKa[3]		0.12 [SD 0.15]
		11	DALKm[3]		0.23 [SD 0.17]
Jones, 2009	UK	1136	PK	24	0.24 [SD 0.25]
		234	DALK	24	0.24 [SD 0.40]
Jensen, 2010	Denmark	61	PK	324 (mean)[2]	46% $\geq$ 0.5 decimal (mean not given)
Sarnicola, 2010	Italy	94	pdDLAK[3]	30 (mean)[2]	0.10 (approx.)[1]
		139	dDALK[3]		0.10 (approx.)[1]
Larkin, 2011	UK	572	PK	24	0.3 (median)
Smadja, 2012	France	32 (20)	DALK	12	0.10 (approx.)[1]

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

time and general protocol.

Studies carried out at the Tennent Institute of Ophthalmology in collaboration with Glasgow Caledonian University show that the visual outcome of keratoplasty in the West of Scotland compares favourably to that reported for the whole of the UK, with nearly three quarters achieving visual acuity of 0.3 logMAR (Snellen 6/12 or 0.5) or better. This is a higher proportion than that previously reported by our group for a smaller cohort of DALKs ($n = 18$) that were performed for herpes simplex keratitis (50% of grafts) (Awan, Roberts, Hegarty, & Ramaesh, 2010). The proportion is also higher than that reported for a cohort that included a relatively high number of repeat grafts, where 40% of cases achieved 0.3 logMAR or better after five years (Beckingsale, Mavrikakis, Al-Yousuf, Mavrikakis, & Daya, 2006). The Glasgow studies indicate that poor visual outcome (e.g. worse than 1.0 logMAR, equivalent to Snellen 6/60 or 0.1) was relatively rare, although the results should be interpreted carefully because grafts with substantial oedema were not included in the analysis.

The mean best corrected visual acuity (BCVA) for grafts performed in Glasgow for a mixture of indications was 0.35 logMAR, which is slightly poorer than the visual outcome reported by the UK-based National Health Service Blood and Transplant register (Jones et al., 2009). This slight difference is likely to be caused by four outliers that were noted in the Glasgow dataset.

Excluding these outliers from the analysis provided a mean BCVA of 0.29±0.24 (range 0.1 to 1.0), which is very similar to the data reported for the whole of the UK (mean BCVA of 0.26) (Jones et al., 2009). Another very recent UK-wide study reported BCVA of 6/12 (0.3 logMAR, 0.5 Snellen decimal) in 36 to 84% of grafts, where those grafts that were performed for keratoconus were shown to have the highest proportion of BCVA better than 6/12 (Larkin et al., 2011). Data from Glasgow support this observation, with 78% of the grafts carried out for keratoconus achieving BCVA of 6/12 (0.3 logMAR) or better.

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

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 outcome, 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 from 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 devel-

oping 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; McCarey, 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; McCarey et al., 2008). After PK, the number of endothelial cells declines at an increased (exponential) rate of 4.2% per year between the fifth an 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.
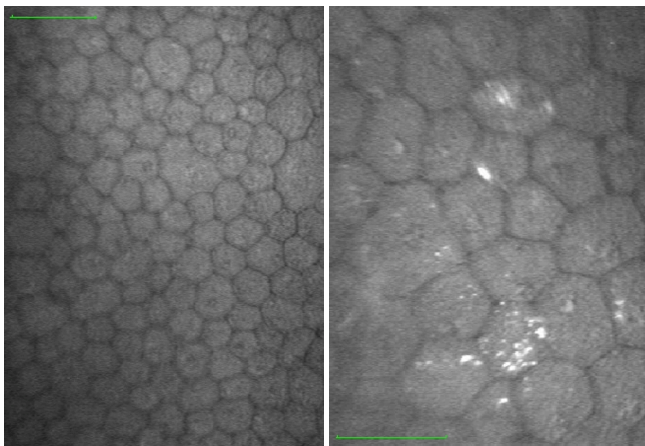

Figure 1: Representative post-operative endothelial confocal image obtained 6 months after DALK (A) and 6 months after PK (B). Scale bar = 50 micrometers; from Jonuscheit et al., *Clin Exp Optom* 2013; with permission.

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/mm^2 (Jonuscheit et al., 2011) and similar values have been reported by other groups for patients treated with DALK (Fontana et al., 2007).
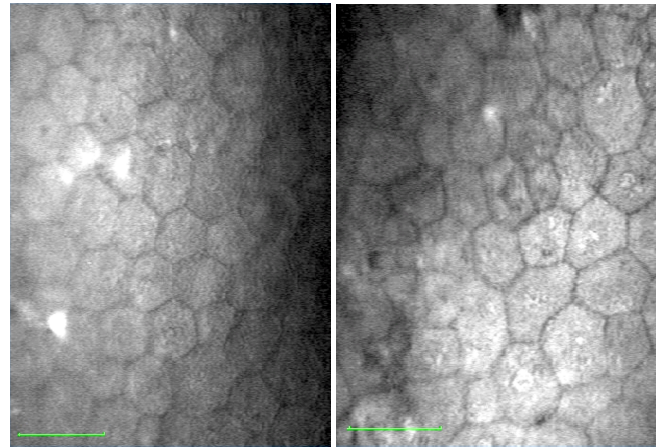

Figure 2: Representative post-operative endothelial confocal images 5 years after DALK (A) and 5 years after PK (B). Scale bar = 50 micrometers; from Jonuscheit et al., *Clin Exp Optom* 2013; with permission.

However, following penetrating keratoplasty the endothelial cell density can vary widely with reported values ranging from 320 to 1980 cells/mm^2 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/mm^2) 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/mm^2 (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 under way at Glasgow to establish if 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.

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