

Longterm follow-up of penetrating keratoplasty for keratoconus

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ABSTRACT.

Purpose: This study aims to describe the current visual and refractive status of patients who underwent penetrating keratoplasty (PK) for keratoconus > 20 years ago and to report on the current status of their grafts.

Methods: A total of 138 eyes in 103 patients were grafted for keratoconus between August 1968 and December 1985. Patients who had not undergone retransplantation were invited to attend a clinical examination. Forty-eight patients (with 61 grafts) accepted the invitation and were examined.

Results: The average length of time since PK was 26.9 years (standard deviation [SD] 4.2 years, range 20.8–38.0 years, $n = 61$). The average graft age at examination was 82.1 years (SD 19.9 years, range 41–115 years). A total of 80% (49 of 61 grafts) of the examined eyes had a clear graft and 46% (28 of 61 eyes) had best spectacle-corrected visual acuity (BSCVA) ≥ 0.5 . The mean endothelial cell density per mm^2 was 894 (SD 4.6, range 470–1775). The mean central corneal thickness of the clear grafts was 0.565 mm (SD 0.048 mm).

Conclusions: Penetrating keratoplasty for keratoconus has a good longterm prognosis; half of the eyes examined in this study had BSCVA ≥ 0.5 at > 20 years after surgery.

Key words: corneal thickness – endothelial cell density – keratoconus – longterm results – penetrating keratoplasty

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Introduction

Keratoconus is a corneal ectasia that has been well described, although its aetiology remains unknown and is possibly multifactorial. Keratoconus may very well represent a final path common to a variety of different pathological processes (Edwards et al. 2001). Nielsen et al. (2007) have estimated the prevalence of keratoconus in Denmark to affect 86 per 100 000 residents.

Keratoconus is a frequent indication for penetrating keratoplasty (PK), but the percentage of PK operations carried out for keratoconus varies between countries and ranges from 16% in Canada to 47% in Italy (Fasolo et al. 2006). Ing et al. (1998) found the risk of graft failure to be 4% over 10 years in keratoconus patients, but up to 54% in other diagnostic groups. In keratoconus, PK is often performed in relatively young

subjects and therefore the longterm results are important. So far, the longest reported average follow-up time after PK in a group of keratoconus patients is 20 years (15–25 years) (de Toledo et al. 2003). The purpose of this study was to assess graft outcomes in keratoconus patients > 20 years after PK.

Materials and Methods

The systematic registration of donors, recipients, surgeries and patient records means that information is available on more than 3000 corneal transplantations performed in the Department of Ophthalmology, Aarhus University Hospital using tissue delivered from the Danish Cornea Bank (which officially opened in May 1978). This archived information and the examination of previous keratoconus patients form the basis of the present study.

The inclusion criteria for this study demanded a minimum of 20 years since PK for keratoconus. The same surgeon (NE) performed 787 PKs between August 1968 and the end of December 1985. In 138 eyes of 103 patients (69 men, 34 women), the indication for PK was keratoconus. Thirty-two patients were excluded for the reasons shown in Fig. 1. Of the remaining 71 patients, 23 did not accept the invitation for examination. Thus 48 patients (61 eyes) were examined (32 men, 16 women).

Figure 1 shows a flow diagram of the transplanted eyes. No primary

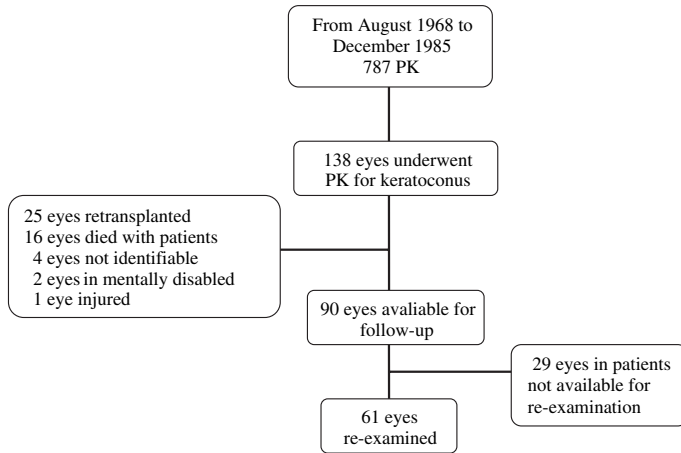


Fig. 1. Flow diagram for the keratoconus re-examination programme, showing numbers of eyes. PK = penetrating keratoplasty.

graft failures were observed. As shown, 18% (25 of 138 grafts) underwent retransplantation. According to the National Patient Registry, the 29 grafts (21%) in the 23 patients who did not accept the invitation for re-examination had not been retransplanted.

The processing of donor tissue changed over the years. The majority of corneas (51) had been used ‘fresh’ (Sperling et al. 1981). Four corneas had been cryopreserved (and were re-examined by Corydon et al. [2009]) and six corneas had been organ-cultured in Eagles minimum essential medium (Sperling 1981). Host bed and donor graft were always identical in size (7.00 mm in 53 eyes and 8.00 mm in eight eyes). Donor grafts were punched out from the endothelial side using standard trephines. The type of suture material changed over time. Interrupted 8-0 silk sutures were used in four eyes and a combination of interrupted silk sutures and a single running 10-0 nylon suture was used in seven eyes. However, a single running 10-0 nylon suture was used in the majority (50) of eyes. Viscoelastics were not used during surgery. Most operations were preformed under local anaesthesia.

The dose and timing of postoperative treatment was only slightly modified over time. The essential treatment was chloramphenicol; prednisolone ointments were applied four times daily and systemic prednisone was tapered over 3 months. The average time before suture removal was 501 days (19–1724 days). All patients

were examined by LBJ at the Department of Ophthalmology, Aarhus University Hospital. Patients were asked not to use contact lenses for the 2 days prior to examination.

The examination included measurement of best spectacle-corrected visual acuity (BSCVA) (using a Möller-Wedel auto-phoropter with Snellen-like optotypes; Möller-Wedel GmbH, Wedel, Germany), intraocular pressure (IOP) (using an average of three measurements in each eye taken with an XPERT NCT Advanced Logic Tonometer; Reichert Ophthalmic Instruments, Depew, NY, USA) and keratometry (Nikon NRK-8000 or Retinomax K-plus2; Nikon Corp., Tokyo, Japan). Central corneal thickness (CCT) was measured optically with a modified Haag-Streit slit-lamp (Haag-Streit AG, Köniz, Switzerland) (Ehlers & Sperling 1977) and an optical low-coherence reflectometer (OLCR; Haag-Streit AG).

Corneal topography was measured with the Humphrey Atlas™ topographer (Carl Zeiss Meditec AG, Jena, Germany). Two topographic indices were calculated and registered: the corneal irregularity measure (CIM) and the corneal shape factor (CSF). A CIM > 1 is considered abnormal; the higher the value, the more irregular is the surface of the cornea. The CSF describes the overall asphericity of the cornea. Values from -0.1 to 0.5 are considered normal; a value lower than -0.1 indicates an abnormally oblate corneal surface; a value > 0.5 and < 1.0 indicates an abnormally prolate surface, and values > 1.0 are indica-

tive for keratoconus (according to the Atlas™ instruction manual).

Specular endothelial microscopy was performed using the Topcon SP-1000 (Topcon Corp., Tokyo, Japan) and endothelial cell density was calculated. Slit-lamp examination was performed and grafts were classified as clear or unclear and as well-adapted or maladapted (reflecting a severe mismatch of recipient–donor thickness). Finally, the patients were asked about their use of optical aids in the operated eye and whether keratoconus was present in the family. Statistical analyses included comparison of graft astigmatism in well-adapted and maladapted grafts (Student’s *t*-test). The local ethics committee approved the examination as a quality control and the study followed the tenets of the Helsinki Declaration II.

Results

Details of the donors and recipients and grafts are listed in Table 1. The average age of the graft (individual donor age at the time of surgery plus follow-up time) was 82.1 years. Table 2 shows the numbers of clear and unclear, and well-adapted and maladapted grafts and indicates that 80% (49 of 61) of the examined grafts were clear. Of the examined grafts (Table 2), 48% appeared to be well-adapted at > 20 years after surgery. In all misaligned grafts the irregularity was located in the inferior half of the circumference.

Figure 2 shows the distribution of BSCVA. A total of 46% (28 of 61) of eyes had BSCVA ≥ 0.5. Of the eyes with BSCVA < 0.5, 42% (14 of 33) had other eye diseases that might potentially reduce vision. In daily life, patients mainly used spectacles (32 patients). Seven patients used contact lenses (three used rigid gas-permeable lenses, one used soft lenses and three used a ‘piggy-back’ combination of hard and soft lenses). Three patients used a combination of contact lenses and spectacles. Six patients did not use any refractive correction at distance. The subjective refractive astigmatism in maladapted grafts was -5.87 D (standard deviation [SD] 2.22), compared with -4.80 D (SD 2.49) in grafts with no misalignment. This difference was not statistically significant (*p* > 0.05).

Table 1. Demographic, refractive and biological parameters in grafts > 20 years after penetrating keratoplasty for keratoconus.

Parameter	Mean	SD	Range	Eyes, <i>n</i>
Donor age, years	55	21.6	12–89	61
Recipient age, years	29	8.6	15–49	61
Time with sutures in the graft, days	501	286	19–1724	60
Graft age (donor age + follow-up time), years	82.1	19.9	41–115	61
Follow-up time, years	26.9	4.2	20.8–38.0	61
Subjective spherical equivalent, D	– 4.68	6.63	– 25.25 to + 14.00	58
Subjective cylinder, D	– 5.39	2.38	0.00 to – 8.00	58
Autorefractive cylinder, D	– 9.25	5.98	– 1.13 to – 25.70	54
Topographic cylinder, D	–8.89	5.62	– 1.23 to – 21.80	50
Average <i>K</i> -value (autokeratometry), D	48.53	6.32	40.72–80.63	54
Average <i>K</i> -value (topographic), D	47.98	4.23	39.01–59.95	52
Endothelial cell density (preoperative), cells/mm ²	2956	439	1924–4029	47
Endothelial cell density (re-examination), cells/mm ²	894	4.6	470–1775	53
Intraocular pressure, mmHg	14.6	4.6	5–28	54
Central corneal thickness (manual optical), mm	0.571	0.061	0.450–0.760	59
Central corneal thickness (OLCR), mm	0.575	0.063	0.432–0.776	58

SD = standard deviation; OLCR = optical low-coherence reflectometer.

Table 2. Distribution of clear and unclear grafts, and well- and maladapted grafts at > 20 years after penetrating keratoplasty for keratoconus.

	Well-adapted grafts, <i>n</i>	Maladapted grafts, <i>n</i>	Total
Clear grafts	22	27	49
Unclear grafts	7	5	12
Total	29	32	61

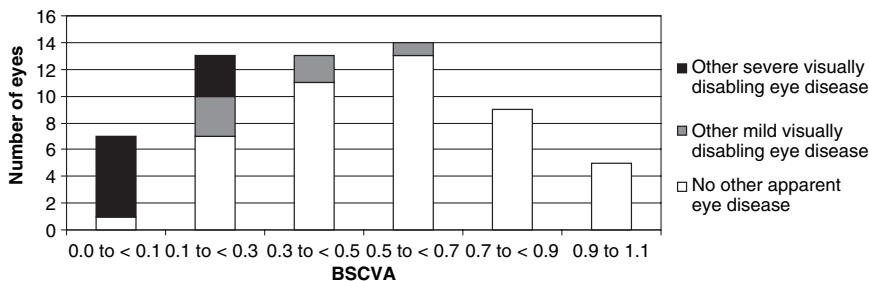


Fig. 2. Best spectacle-corrected visual acuity in 61 eyes grafted for keratoconus > 20 years prior to re-examination.

Corneal topography could be performed in 54 of the 61 eyes. The mean CIM was 6.12 (SD 4.37) and all corneas were classified as irregular as values ranged from 1.70 to 22.76. The CSF revealed that seven eyes (13%) had a normal, spherically shaped cornea, 33 eyes (61%) had an oblate cornea, and 14 eyes (26%) had a prolate corneal shape. No eyes had values > 1.0, such as might be seen in keratoconus.

Of the 48 patients examined, eight had a history of keratoconus in the family. Thirty-five patients were not aware of any family members with keratoconus and five did not know

their family history. The average CCT of clear grafts was 0.565 mm (SD 0.048 mm) when measured with OLCR and 0.560 mm (SD 0.041 mm) when measured optically. The unclear grafts were thicker, with an average CCT of 0.625 mm (SD 0.103 mm) when measured with OLCR and 0.619 mm (SD 0.105 mm) when measured optically.

Discussion

A diagnosis of keratoconus was the indication for 18% of all keratoplasties performed from 1968 to 1985 in Århus, Denmark. Data for PK procedures

performed elsewhere during the same period show that keratoconus accounted for 7.2% of PKs in the Netherlands (Delavalette et al. 1985) and 21% in the USA (Ing et al. 1998).

Demographic data for the keratoconus patients undergoing keratoplasty reported here generally correspond well with equivalent data from other studies. The mean age of the patients at the time of surgery was 29 years, which corresponds well with findings from other studies (Sharif & Casey 1991; Pramanik et al. 2006). In our study, 67% of patients were male and 33% were female; a male preponderance was also reported by Sharif & Casey (1991) and Pramanik et al. (2006). However, Delavalette et al. (1985) described a series in which 56% of patients were female and 44% were male.

Most cases of keratoconus are sporadic and a family history of the disease is typically reported in < 10% of cases (Rabinowitz et al. 1990). In this study, 17% of the subjects were aware of other family members also affected by keratoconus. The long-lasting nature of the disease and the higher age of our study subjects may have made them more likely to be aware of family members with similar disease. Autosomal dominant inheritance with variable phenotypic expression is the expected genetic component of a symptom or disease that is probably multifactorial (Edwards et al. 2001).

The examination was, on average, performed close to 27 years after PK. Because of the length of time that had

elapsed since surgery, a number of patients had died (13%) and many subjects were, for various reasons, unable to attend the examination (32%). Despite these limitations, some estimates of graft survival can be extracted from the present study. In patients alive > 20 years after keratoplasty, 40% of the 122 transplanted grafts were found to be clear. A total of 30% of the operated eyes had either been re-grafted or were found to be unclear at the time of re-examination. The status of 30% of the grafts was unknown. None of the 29 eyes in patients who did not attend for re-examination had been retransplanted.

A total of 80% (49 of 61) of the examined grafts were clear; this finding is consistent with the few other studies of longterm graft survival in keratoconus. In their study of 67 grafts, Paglen et al. (1982) found that slightly < 90% of grafts were clear 20 years after keratoplasty. Pramanik et al. (2006) estimated the 25-year graft survival rate to be 85.4%.

An accelerated loss of endothelial cells is seen after PK. In unoperated eyes, 0.6% of endothelial cells are lost every year (Bourne et al. 1997). Assuming a linear loss, 85 cells/mm²/year (SD 23.5), corresponding to 2.8% per year, were lost in the present series. Ing et al. (1998) found an annual loss of 4.2% of endothelial cells from the fifth to the 10th year after PK. However, it may be that loss of endothelial cells is not linear but bi-exponential, with an initial rapid loss and a later slow loss (Armitage et al. 2003). In theory, a graft must show about 2500 endothelial cells/mm² before transplantation in order to retain > 500 cells/mm² at 30 years after PK (Armitage et al. 2003). In the present study, endothelial cell density was close to 3000 cells/mm² before transplantation, and just < 900 cells/mm² were present at re-examination. These numbers correspond well with the model of Armitage et al. (2003).

It was noted that one patient carried a 115-year-old cornea. Visual acuity in the eye was 0.7 and endothelial cell density was 1775 cells/mm². Both Paglen et al. (1982) and Sharif & Casey (1991) found no relationship between donor age and longterm graft clarity, even when the donor was aged

> 70 years. The visual status of the grafts almost 27 years after PK was fairly encouraging. A total of 46% of the re-examined eyes had sufficient VA to allow the subject to hold a driver's licence, which requires BSCVA > 0.5 under Danish law. This number is slightly lower than figures quoted in studies with shorter follow-up periods, such as 66% in Pramanik et al. (2006).

The percentage of interface maladaptation was 52% (29 of 61 grafts), but maladaptation of the graft was not associated with high cylinder values. de Toledo et al. (2003) found that the keratometric cylinder value started to increase 10 years after PK. After 25 years an average value of - 7.25 D (SD 4.27) was found, corresponding well with values in this study. The increasing keratometric astigmatism is possibly caused by progressive thinning of the host bed (Lim et al. 2004).

Whether or not keratoconus recurs in the donor graft has been debated for many years. A prominent feature of keratoconus is thinning of the corneal stroma. Bourges et al. (2003) found no central corneal thinning, but did find histological changes compatible with the recurrence of keratoconus in grafts removed from keratoconus patients. Pramanik et al. (2006) found recurrence of keratoconus in 5.4% of grafts, with a mean time to recurrence of almost 18 years. In the present study, corneal thickness was normal or even slightly higher than normal, even in clear grafts. Similarly, topographic indices (CSF value) were not indicative of keratoconus. We cannot exclude the possibility that recurrence was present in some retransplanted grafts, but, from this very longterm follow-up study, keratoconus does not appear to recur after keratoplasty.

The present study confirms that PK for keratoconus has a good longterm prognosis and indicates that keratoconus patients undergoing PK have a high chance of retaining a clear cornea with BSCVA > 0.5 at > 20 years after surgery. Today, alternative treatments are being introduced. Progressive corneal ectasia may be halted by corneal cross-linking with ultraviolet-A riboflavin (Wollensak et al. 2003), and intra-corneal ring segments (Ertan & Colin 2007) or topography-based photorefractive keratectomy (Hjortdal et al. 2008) may improve vision and

eliminate or postpone the need for keratoplasty. Despite these efforts, major surgery, possibly in the form of lamellar transplantation (Watson et al. 2004), is still needed in some cases. The longterm results of these 'new' methods are, however, unknown.

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