Clinical outcomes of modern lamellar keratoplasty techniques

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Chapter 8

Bowman layer transplantation: 5-year results

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ABSTRACT

Purpose. To evaluate the 5-year clinical results of isolated Bowman layer (BL) transplantation in the treatment of advanced keratoconus.

Design. Prospective, single-center, interventional case series.

Setting. Tertiary referral center.

Patient. Population: 20 eyes of 17 patients with advanced keratoconus that underwent BL transplantation.

Intervention. An isolated BL-graft was positioned into a manually dissected mid-stromal pocket.

Main Outcome Measures. Scheimpflug-based corneal tomography measurements, best corrected spectacle and contact lens visual acuity (BSCVA and BCLVA), endothelial cell density, and complications up to 5 years after surgery.

Results. Measured simulated and maximum keratometry (Kmean and Kmax) values were stable up to 5 years after surgery (*P*>.105 and *P*>.261, respectively), following an initial decrease from pre- to one month postoperatively (*P*<.001). Mean LogMAR BSCVA remained stable (*P*>.985), after an initial improvement from pre- to 12 months postoperatively (*P*=.026). Mean BCLVA did not change (*P*>.317). During all postoperative follow-ups, mean densitometry values were higher than preoperatively (*P*<.001). A corneal hydrops occurred in one eye at 4½ years postoperatively; no other postoperative complications were observed. Kaplan-Meier analysis showed an estimated success rate of 83% at a mean follow-up of 50 (±16) months. Endothelial cell density remained stable during the entire follow-up period (*P*>.174).

Conclusions and Relevance. After early postoperative corneal flattening, topographies were stable up to five years after BL transplantation, preserving BCLVA and contact lens tolerance, potentially allowing long term postponement of penetrating or deep anterior lamellar keratoplasty.

Keywords: Keratoconus, corneal crosslinking, deep anterior lamellar keratoplasty, progressive ectasia, Bowman layer, pachymetry, corneal transplantation, surgical technique.

INTRODUCTION

Keratoconus is regarded a bilateral, multifactorial corneal disorder characterized by progressive corneal protrusion and thinning, leading to increasing visual impairment due to irregular astigmatism and scarring.[1,2] Although the exact etiology and pathogenesis of keratoconus remains unclear, both genetic and environmental factors may contribute, with reports on involvement of (pro) inflammatory molecules in disease progression as well.[3-5]

So far, keratoconus management consisted of optimizing visual acuity with contact lenses, and in later phases with penetrating keratoplasty (PK) or deep anterior lamellar keratoplasty (DALK).[2,6] Although these keratoplasty techniques may give efficient visual rehabilitation in the short term, long term outcomes are often compromised by adverse events, including suture- or wound-healing related complications, allograft rejection and high irregular astigmatism.[6-8] In eyes with advanced keratoconus, latent ocular surface disease may further increase the risk of complications following PK/DALK owing to the large incisions, sutures, and/or a neurotrophic cornea.[6,7,9]

BL transplantation has recently been introduced as a new treatment option for patients with advanced keratoconus (ineligible for either UV-crosslinking or intracorneal ring segments (ICRS)), to flatten the recipient cornea and to halt progression of ectasia, thereby potentially delaying or avoiding the need for PK/DALK.[10] Previous reports about this new technique described the technical feasibility and the early postoperative course of the treatment.[10,11] These studies demonstrated a corneal flattening of on average 8D in the first postoperative month, followed by a stabilization of the ectasia up to on average 21 months postoperatively.[11]

The aim of the current study was to evaluate the longer term efficacy of isolated BL transplantation in our first case series of 20 eyes.

METHODS

Prospectively collected data of 20 eyes (17 patients; 8 male and 9 female; mean age 31 (±12) years) that underwent BL transplantation between 2010 and 2012 for progressive keratoconus stages III to IV (Table 1),[12] were evaluated up to 5 years postoperatively. All eyes had demonstrated unequivocal keratoconus progression in the year prior to the BL transplantation (defined as ≥1D change in simulated keratometry (SimK) values, ≥2D change in maximum keratometry (Kmax), or both), but were considered ineligible for either UV-crosslinking or ICRS given the corneal steepness or thickness. Since these patients subjectively achieved satisfactory vision with contact lenses, halting progression to preserve the present visual acuity and contact lens tolerance was the main treatment objective.

Table 1. Demographics and baseline characteristics

Number of eyes / patients (n)	20 / 17
Age mean (SD)	31 (±12) years
range	17 – 71 years
Male / Female (n)	8 / 9
Keratoconus grade* (range)	III - IV
Eyes with preexisting corneal scarring (n)	12

n = number; SD = standard deviation; *Keratoconus grading according to Pentacam Topographic Keratoconus Classification.[12]

All patients signed an IRB approved informed consent; the study was conducted according to the Declaration of Helsinki and was registered at www.clinicaltrials.gov (study identifier NCT01686906).

Donor tissue preparation

The procedure for BL-graft preparation has been previously described.[13] BL-grafts were either prepared from whole donor globes (obtained less than 24 hours postmortem, with corneas considered ineligible for PK) or from an anterior corneal button after stripping a Descemet graft.[13] Donor globes were mounted on a globe holder (DORC International, Zuidland, the Netherlands), and anterior corneal buttons were mounted on an artificial anterior chamber (Gebauer Medizintechnik, Neuhausen, Germany; or Katena, Rockmed, Oirschot, the Netherlands) epithelial side up, after which the epithelium was carefully removed using surgical spears. A circular superficial incision was made just within the limbal corneal periphery using a 30-gauge needle. With a single tip of a McPherson forceps (Moria, Medical Workshop, Groningen, the Netherlands), the peripheral BL edge was lifted from the underlying anterior stroma and then grasped with the McPherson forceps or a custom-made forceps (DORC International), thereby carefully stripping the entire BL from its underlying anterior stromal attachments, obtaining a 9- to 11-mm diameter BL-sheet.[13] Because of the inherent elasticity of the tissue, BL-grafts spontaneously curled into a single or double roll with the epithelial border at the outside. The BL-roll was submerged in ethanol 70% to remove remaining epithelial cells and stored in organ culture medium (CorneaMax; Eurobio, Courtaboeuf, France) at 31°C until the time of transplantation.[13]

Surgical technique

As previously described, BL transplantations were performed by two experienced surgeons (GM, ID) under local anesthesia (4 ml 1% ropivacain hydrochloride with 150IU Hyason), with the patient positioned in anti-Trendelenburg position, after an ocular massage and a Honan's balloon for 10 minutes.[10,11] With the anterior chamber filled with air, a manually dissected mid-stromal pocket was created over 360° up to the limbus, as described for manual DALK.[14] The BL-graft was again immersed in 70% ethanol for 30 seconds in order to remove all remnant cellular material, after which it was thoroughly rinsed with BSS and stained with trypan blue 0.06% (VisionBlue™, DORC International). Most air was then removed from the anterior chamber, and the graft was carefully inserted into the stromal pocket with the epithelial side facing up using a glide (BD Visitec™ Surgical Glide, Beaver-Visitec International, Waltham, USA), centered and unfolded, after which the eye was pressurized.[10,11] Postoperative medication included chloramphenicol 0.5% six times daily and dexamethasone 0.1% four times daily for 1 month, followed by fluorometholone 0.1% four times daily, tapered to one time daily over a period of 1 year, after which the use was discontinued. Surgical procedures were recorded on DVD (Pioneer DVR-RT601H-S, Tokyo, Japan).

All eyes underwent complete ophthalmological evaluation before and at set time-points after the surgery. Best corrected visual acuity (BCVA), slit-lamp biomicroscopy, endothelial cell density, and Scheimpflug-based corneal tomography (Pentacam HR; Oculus, Wetzlar, Germany) of the preoperative visit and 1 month and 1, 2, 3, 4 and 5 years postoperative examinations were used for evaluation. If the central endothelium could not be visualized because of central corneal scarring, paracentral images were analyzed. Postoperative complications were recorded.

Best spectacle- and contact lens-corrected visual acuities (BSCVA and BCLVA, respectively) were assessed under mesopic light conditions with a Snellen letter chart and acuities were converted to LogMAR units for statistical analyses.

During Pentacam examination, the automatic release mode was used to eliminate operator-induced errors. Only images of sufficient quality of the front and back corneal surfaces were used (scans with an error message other than 'model' were rejected) for evaluation. Pentacam parameters included central corneal thickness (CCT), thinnest point pachymetry (TPT), maximum keratometry (Kmax), mean simulated keratometry (Kmean) and backscattered light. Backscattered light of total corneal diameter was evaluated in 3 different fixed corneal depths (anterior layer [anterior 120 μm], central layer, posterior layer [posterior 60 μm]), using the "corneal densitometry" display of the Pentacam, and quantified on a scale from 0 (no obscuring) to 100 (completely opaque). To standardize ambient light conditions, all measurements were performed in a windowless clinical assessment room with a uniform ambient light level of 4 lux as measured by a luxmeter (Voltcraft BL-10 L Luxmeter; Conrad Electronic SE, Hirschau, Germany). Additionally, it was analyzed whether the "background" gray scale outside the cornea of the preoperative and postoperative Pentacam examinations was stable over time for randomly selected cases.

Kaplan Meier survival analysis was performed to estimate the success probability of BL transplantation. Success was defined as stabilization (no further steepening of the corneal curvature), and absence of complications. Linear mixed models (using IBM SPSS Statistics 24), with age and gender as covariates, were used to assess how Kmax, Kmean, CCT, TPT, BCVA, and densitometry values evolved over time. Contrast tests were used to establish a time-point of stabilization (densitometry) or to assess whether evaluated parameters changed after the previously reported time-point of stabilization, which was at 1 months follow-up for most parameters (except for BSCVA, that showed improvement up to 1 year after BL transplantation).[11] All multiple tests were controlled for false discovery, and all *P*-values represent adjusted *P*-values. A *P*-value of <.05 was considered statistically significant.

RESULTS

Of the 20 eyes evaluated before and after BL transplantation, two eyes were lost to follow-up at 18 months and 4 years after surgery and one eye underwent cataract surgery (for senile cataract development (71 year-old patient) considered unrelated to BL transplantation) just after the 3 years follow-up. Hence, 19 eyes were available up to 3 years of follow-up, and 17 eyes up to 5 years of follow-up.

After the previously reported initial improvement in mean BSCVA from preoperative to 12 months after surgery (1.27 (±0.44) LogMAR to 0.90 (±0.30) LogMAR, (*P*<.001), representing an improvement in Snellen equivalent of 3/60 (0.05) to 20/150 (0.13)),[11] no further changes occurred (*P*>.05) (Table 2). Of the 13 eyes with BSCVA data available at 5 years, 5 eyes (38%) showed an improvement of 2 Snellen lines or more and 2 eyes (15%) of 1 line, 4 eyes (31%) remained stable and 2 eyes (15%) showed a decline of 1 line compared to preoperative values. Mean BCLVA was stable from preoperative up to the latest postoperative time-point (*P*>.318) (Table 2). At 5 years after surgery, 11 of 15 eyes (73%) had a BCLVA of 20/40 or better (≥0.5), while before surgery 9/18 (50%) reached 20/40 or better (≥0.5).

TPT showed an increase at 2 years after surgery (estimated mean difference (Δm)=33μm, standard error (SE)=10, *P*=.037); at all other time-points differences were not statistically significant (*P*>.053). CCT showed no change from before to after BL transplantation or between follow-ups (*P*>.055) (Table 2). One eye, with stable keratometry values and BCVA, showed a decrease in both TPT and CCT of >5% at 3-5 years compared to preoperatively, while in all other eyes pachymetry values remained stable.

At 5 years after surgery, mean Kmax and Kmean were -6.9 diopters (D) (SE= 1.2, *P*<.001) and -4.1D (SE= 0.8, *P*=.001) flatter than before surgery (Table 2). Both parameters remained stable after the initial flattening at 1 month postoperatively (*P*>.262 and *P*>.105, respectively) (Table 2 and Figure 1). Continued steepening of Kmax and Kmean despite BL transplantation was observed in 2/20 cases (10%). One of these patients (40 year-old

Table 2. Distribution of clinical outcome measures during follow-up visits

		Preoperative* Mean ± SD	Postoperative follow up Mean ± SD					
			1 month*	1 year*	2 years	3 years	4 years	5 years
BSCVA	LogMAR	1.27 (±0.44)	1.13 (±0.37)	0.90 (±0.30)†	1.05 (±0.49)	1.15 (±0.57)	1.13 (±0.51)	0.95 (±0.48)
	Snellen range	1/60 – 20/80 n=19	1/60 – 20/100 n=19	3/60 – 20/67 n=15	1/60 – 20/50 n=15	1/60 – 20/67 n=11	1/60 – 20/33 n=10	1/60 – 20/33 n=13
BCLVA	LogMAR	0.33 (±0.19)	n.a.	0.39 (±0.18)	0.35 (±0.15)	0.35 (±0.15)	0.35 (±0.17)	0.34 (±0.17)
	Snellen range	20/100 – 20/20 n=18	n.a.	20/133 – 20/25 n=19	20/100 – 20/25 n=17	20/100 – 20/25 n=19	20/100 – 20/25 n=15	20/100 – 20/25 n=15
Pachymetry (μm)	Thinnest point	332 (±59)	363 (±56)	351 (±46)	366 (±56)†	351 (±56)	348 (±51)	346 (±49)
	Central point	397 (±57) n=20	415 (±65) n=19	423 (±56) n=19	431 (±60) n=18	420 (±62) n=19	417 (±53) n=16	409 (±53) n=16
Kmax (D)		77.2 (±6) n=20	69.2 (±4)† n=19	70.8 (±5)† n=19	72.1 (±5)† n=18	71.6 (±5)† n=19	71.4 (±5)† n=16	70.3 (±5)† n=16
Kmean (D)		64.0 (±6) n=20	58.9 (±4)† n=19	60.6 (±5)† n=19	61.1 (±5)† n=18	61.3 (±5)† n=19	60.7 (±6)† n=16	59.9 (±6)† n=16
Densitometry (GSU) (0 – 12 mm)	Anterior 120 μm	25 (±5)	27 (±5)	27 (±5)	31 (±8)†‡	29 (±4)†	31 (±4)†‡	31 (±6)†‡
	Central	17 (±3)	22 (±4)†	21 (±4)†	23 (±4)†	23 (±4)†	23 (±3)†	24 (±4)†
	Posterior 60 μm	14 (±2)	19 (±3)†	17 (±3)†‡	17 (±3)†	17 (±3)†	17 (±3)†	17 (±3)†
	Total thickness	19 (±3) n=20	23 (±4)† n=19	21 (±4)† n=19	24 (±5)† n=17	23 (±3)† n=19	24 (±3)† n=16	25 (±4)† n=16

BSCVA = best spectacle-corrected visual acuity; BCLVA = best contact lens corrected visual acuity; D = Diopters; GSU = grey scale units; Kmax = maximum keratometry; Kmean = mean simulated keratometry; n = number of eyes; SD = standard deviation.
† statistically significant change compared to preoperative (*P*<.05)
‡ statistically significant change compared to 1 month FU (*P*<.05)
* previously reported data (except for densitometry data)[11]

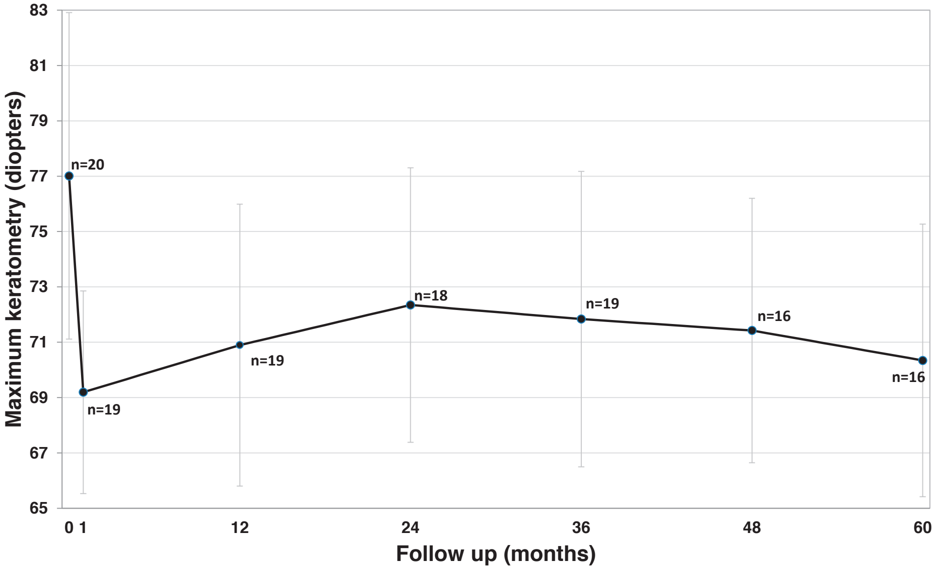

Figure 1. Graph displaying the postoperative evolution of maximum keratometry (Kmax). Note the distinct decrease in Kmax in the first postoperative month, followed by relative stabilization up to 5 years after Bowman layer transplantation.

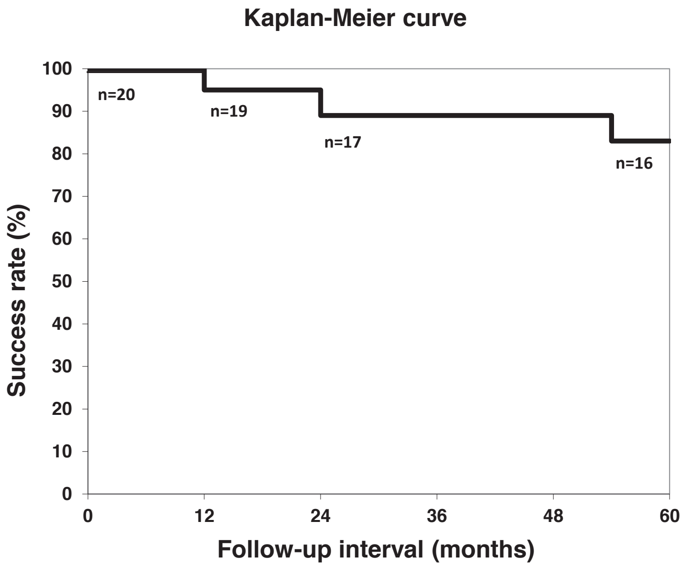

Figure 2. Kaplan-Meier curve representing the postoperative success rate of the 20 included Bowman layer transplantation cases. During the first year after surgery one eye showed continued steepening of maximum keratometry, all other eyes showed stabilization. In the second postoperative year another eye showed progression of the ectasia. At 4 ½ years after Bowman layer transplantation, one eye (without any signs of earlier progression) presented with a corneal hydrops. The cumulative success rate at 50 (±16) months was calculated to be 83%.

male) had a very thin preoperative pachymetry (TPT 236μm and CCT 300μm) and the other patient (31 year-old male) admitted continued, frequent eye rubbing.

Another 33 year-old male patient with a history of eye rubbing and atopy presented with an acute corneal hydrops at 4½ years (53 months) postoperatively. Topical treatment with dexamethasone 4 times daily (tapered over 4 months) and NaCl 5% at night resulted in continuous corneal clearing with some residual scarring, and visual acuity restored to pre-corneal hydrops levels (BCLVA 20/50). No postoperative complications were observed in any of the other cases. Categorizing the two eyes with progressive steepening and the one eye with corneal hydrops as 'failures', Kaplan-Meier analysis showed an estimated success rate of 83% at a mean follow-up of 50 (±16) months (Figure 2). None of the eyes in our study required PK/DALK up to the latest follow-up.

Compared to preoperative values, densitometry values at the 1 month follow-up showed an elevation in the central and posterior corneal layers ($P<.001$), and stabilization thereafter ($P>.102$). For the anterior 120μm of the cornea, which showed no changes up to the 1 year follow-up ($P>.99$), an increase from 1 to 2 years after surgery was observed ($P<.016$). Until the latest follow-up, all densitometry values remained higher than preoperatively ($P<.001$) (Table 2 and Figure 3).

Mean endothelial cell density did not change from before surgery (2600 (±452) cells/mm^2) up to five years postoperatively (2589 (±449) cells/mm^2; $P>.319$).

DISCUSSION

Clinical outcomes up to an average of 21 (±7) months after BL transplantation of this series of eyes were reported previously;[11] two cases from that initial series of 22 eyes were excluded from this current longer term postoperative evaluation because of (previously reported) intraoperative perforations of the Descemet membrane, resulting in an inability to complete the operation properly.[11]

In our current study, the clinical outcome in eyes that underwent BL transplantation between 2010 and 2012 were evaluated to present the five-year outcomes of the procedure. All but 3/20 eyes were considered successful, with typically a substantial corneal flattening immediately after surgery, and corneal curvature remaining unchanged thereafter, while acceptable contact lens vision and tolerance were preserved. Within the five-year follow-up period, keratoconus disease progression and/or severe complications could be avoided in 83% of the eyes, while none of the eyes required retransplantation, e.g. PK or DALK. Hence, the outcome may be promising given reported failure rates after UV-crosslinking of 8 to 33% at 1 and 3 years postoperatively, [15-20] with possibly a higher risk for keratoconus progression in more advanced cases.[21,22]

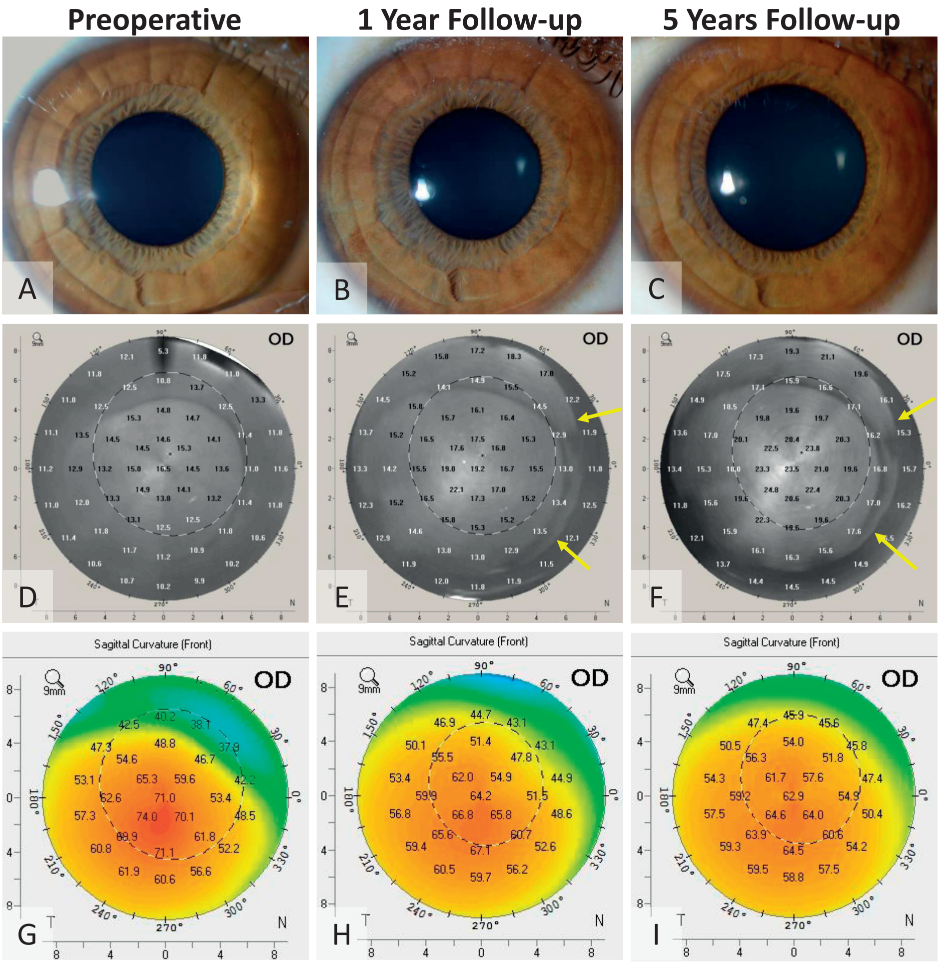

Figure 3. Slit-lamp images (A-C), average corneal densitometry displays (D-F), and anterior corneal topography maps (G-I) of an eye before (A, D, G) and 1 (B, E, H) and 5 years (C, F, I) after Bowman layer transplantation. Note that the cornea is clear preoperatively (A), as well as postoperatively at 1 and 5 years (B, C). There is a slight increase in densitometry between preoperative (D) and postoperative time-points (E, F), probably due to the introduction of the Bowman layer graft (the yellow arrows indicate the Bowman layer-graft edge). The difference between the densitometry maps at 1 (E) and 5 years (F) after surgery represents the observed densitometry increase in the anterior corneal layers. A flattening of the corneal topography (G-I) can be noticed from preoperative (G) to the 1 year follow-up (H), and stabilization thereafter (H-I).

Although the reported 5-year graft survival estimates after PK and DALK for keratoconus may be around 97% and 99%, respectively,[23,24] the long-term postoperative course of these techniques is not infrequently compromised by several adverse events.[6-8,24-27] In contrast, the low postoperative complication rate observed during the 5-year period after BL transplantation may be a major advantage, possibly owing to the fact that no corneal surface incisions or sutures are involved with BL transplantation, minimizing, if not diminishing the risk of short- and long-term wound healing-, suture related-, and ocular surface problems. Furthermore, since the BL-graft is acellular, the risk of allograft rejection may be minimal, which permits a lower postoperative steroid burden, thereby reducing the occurrence of steroid-related complications such as cataract and glaucoma.

Surprisingly, in one eye, an acute corneal hydrops had developed at around 4½ years after BL transplantation, without prior signs of keratoconus progression. The patient, however, had a history of eye rubbing and severe allergic episodes, which have been identified as risk factors for the development of hydrops in keratoconus, even after UV-crosslinking.[28,29] Therefore, also after keratoconus treatment, patients should be counseled about the possible impact of eye-rubbing, and allergies may need closer monitoring.

Attributed to the midstromal dissection and positioning of a BL-graft into the midstroma of a host cornea, corneal backscattering (densitometry) may increase through irregularities in the interface and/or differences in refractive indices between the BL-graft and the host-stroma. In a previous report on corneal densitometry in 15 eyes up to one year after BL transplantation, an increase in densitometry in the central and posterior layers of the cornea was found, while the anterior cornea remained stable.[30] These findings could be confirmed in the current analysis. However, while after the first postoperative year the densitometry of the central and posterior corneal layers remained stable, anterior densitometry showed an unexpected increase. Still, since objectively, as well as subjectively no visual decrease or symptoms were noticed during the study period, the clinical impact of this rise in corneal densitometry may be minimal. Surveys concerning subjective visual outcomes and contrast sensitivity analysis may be helpful in clarifying the effect of corneal backscattering on the optical quality after BL transplantation.

Increasing anterior corneal densitometry values have also been found with advancing age or corneal disease.[31,32] Given that the increase in anterior corneal densitometry in our study group was only noticed between the 1- and 2-year follow-up, with stabilization again thereafter, advancing age or disease progression does not seem a logical explanation for our finding. Repeatability of densitometry measurements were reported to be worse in eyes with keratoconus, compared with healthy control eyes, and the anterior corneal region seems to have the lowest densitometry repeatability.[33] The reliability of the anterior corneal densitometry values of our relatively small study group may consequently be somewhat questionable, especially when considering the keratoconus stage of the included eyes with presence of preexisting corneal scarring in more than half of cases.

Apart from the fact that corneal densitometry values may have been less reliable, keratometric measurements have also shown to be less reproducible in advanced keratoconus cases,[34] which may be observed as 'intra-individual' keratometry variability between measurements. Consequently, keratoconus progression or stabilization may be more difficult to recognize in advanced keratoconus cases, and hence in the current patient group. Another limitation of this study may be the absence of a control group. Nevertheless, despite the 'intra-individual' variabilities, following the initial corneal flattening seen at 1 month postoperatively, a clear stabilizing trend could be recognized during the 5 years of follow-up after BL transplantation in these preoperatively progressing advanced keratoconus cases.

Therefore, this unique case series shows that BL transplantation is a potential treatment option to stabilize ectasia over a longer period in eyes with progressive, advanced keratoconus, while the risk for complications is minimal.

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