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Femtosecond Laser-Assisted Deep Lamellar Endothelial Keratoplasty: A New Approach to a Forgotten Technique

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Purpose: To review indications and clinical results for a hybrid deep lamellar endothelial keratoplasty (Femto-DLEK) technique combining contemporary donor tissue preparation and implantation techniques with femtosecond laser-assisted dissection of the host tissue.

Methods: A retrospective analysis of consecutive cases of Femto-DLEK performed between 2011 and 2014 at Moorfields Eye Hospital, London, was conducted. All patients underwent manifest refraction and optical coherence tomography examination at their most recent review visit. Secondary interventions, graft rejection, and graft failure were recorded alongside corrected distance visual acuity.

Results: Femto-DLEK was performed in 7 eyes of 7 cases. Mean postoperative follow-up duration was 19 months. Indications included revision of deep anterior lamellar keratoplasty (n = 4), revision of failed Descemet stripping endothelial keratoplasty in cases with an anterior chamber intraocular lens (n = 2), and primary surgery in cases of dense posterior stromal copper deposition. All corneas were recorded as clear by 6 weeks after surgery. Median (range) preoperative corrected distance visual acuity was 6/60 (6/9–1/60), which improved to 6/9 (6/6–6/24) at final review. Tissue bridges requiring significant additional manual lamellar dissection were present in all 4 cases in which deep stromal femtosecond laser lamellar dissection was performed. Femtosecond laser host dissection in the remaining cases was restricted to only a posterior side-cut.

Conclusions: Femto-DLEK is a useful alternative endothelial keratoplasty modality for a narrow range of indications. The femtolaser posterior side-cut facilitates DLEK, but further development of the Femto-DLEK technique is required to optimize the combination with deep lamellar host dissection.

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Posterior lamellar keratoplasty was originally described by Melles in 1998.[1] The surgery was later modified by Terry in 2001 and was termed deep lamellar endothelial keratoplasty (DLEK).[2–4] In DLEK, the failed endothelium, Descemet membrane, and a thin lamella of the posterior corneal stroma are replaced by a healthy disc of donor corneal tissue, which is positioned in the reciprocal host dissection. Manual host lamellar dissection in DLEK is time consuming, and the posterior side-cut, in particular, is technically challenging if performed through a 6-mm or smaller pocket without a reverse trephine as in later iterations of the DLEK technique. Femtosecond laser-assisted tissue preparation was used by a number of investigators to simplify corneal tissue dissection.[5,6] However, DLEK was largely abandoned in favor of Descemet stripping techniques, which do not require host stromal dissection. These include Descemet stripping endothelial keratoplasty,[7,8] Descemet stripping automated endothelial keratoplasty (DSAEK),[9] and Descemet membrane endothelial keratoplasty (DMEK).[10]

DLEK is now a largely forgotten endothelial keratoplasty modality; but it can still be useful for a limited but distinct set of indications. Femtosecond laser donor preparation in endothelial keratoplasty did not gain popularity, at least in part, because of limited access to technology.[11] Most eye banks use microkeratomes to precut endothelial keratoplasty donor lenticules.[12] Femtosecond lasers are now widely available, and the timing may be right for reevaluation of their possible role in facilitating host dissection for DLEK. In this study, we document the anatomical and functional outcomes from an exploratory case series of femtosecond-assisted DLEK (Femto-DLEK), combining femtosecond laser-assisted host tissue dissection with conventional microkeratome donor tissue preparation and injection techniques.

MATERIALS AND METHODS

The records of 7 consecutive eyes operated on by a single surgeon (B.D.A.) at the study hospital between 2011 and 2014 were analyzed retrospectively. This study was

approved as an audit project by the Clinical Audit Working Group at Moorfields Eye Hospital, London.

Local anesthesia with sedation was used for all surgeries. The 150-kHz IntraLase iFS femtosecond laser (AMO Inc, Irvine, CA) was used in the single-pass mode for the recipient corneal lamellar dissection by creating a posterior intrastromal lamellar cut of 7.5 to 9.0 mm in diameter at 400 to 450 μm depth (Fig. 1A, *), depending on the preoperative corneal pachymetry as measured by the Visante anterior segment optical coherence tomography (Carl Zeiss, Germany). An intersecting posterior side-cut of 7.0 to 8.5 mm of diameter was used in all cases (Fig. 1A, **). The femtosecond laser parameter settings used are summarized in Table 1. In 1 case, the lamellar cut was performed by manual dissection at approximately 75% to 85% of corneal thickness through a 5.0-mm superior scleral incision, using a combination of blunt dissection with the Morlet lamellar dissector (Duckworth & Kent, England) and sharp dissection with a Crescent knife (Alcon). In 2 cases, the posterior side-cut was performed in isolation as deep lamellar dissection had already been performed during previous deep anterior lamellar keratoplasty (DALK). The dissected posterior recipient disc was removed from the anterior chamber through a 3.2- to 4.5-mm limbal incision placed temporally (Fig. 1B). A 7.0 to 8.5 mm DSAEK or DMEK graft provided by Moorfields Lions Eye Bank (Moorfields Eye Hospital, London, United Kingdom) was then inserted using the EndoSaver injector system (Ocular Systems Inc, Winston Salem, NC), unfolded within the anterior chamber and positioned within the reciprocal host dissection using a standard DSAEK technique,[7–9] then maintained in position with 100% anterior chamber air fill at physiological intraocular pressure for 10 minutes after incision closure with interrupted 10-0 nylon suture. Preoperative pupil dilation was used in all cases to prevent pupil block. We did not perform peripheral iridotomy. The air fill was reduced to approximately 60%, and the anterior chamber was refilled with balanced salt solution to restore physiological intraocular pressure using a "no chamber collapse" iterative air–fluid exchange technique (Fig. 1C). Subconjunctival cefuroxime (125 mg) and betamethasone (5 mg) were injected to conclude each case. All patients postured face-up-to-ceiling for 30 minutes before discharge. Postoperatively, they received a 1-week course of topical antibiotics (chloramphenicol 0.5%) and a diminishing regimen of topical steroids (dexamethasone 0.1% hourly week 1, 4 times daily for 6 months, twice daily for 3 months, once daily for 3 months; then fluorometholone 0.1% once daily for 1 year) for a minimum of 2 years. At their last review during the study period, all patients underwent manifest refraction and anterior segment optical coherence tomography.

TABLE 1. Laser Specifications for the Preparation of the Recipient Cornea

Lamellar Cut		Posterior Side-Cut	
Parameter	**Value**	**Parameter**	**Value**
Diameter, mm	7.5–9.0	Diameter, mm	7.0–8.5
Depth, μm	400–450	Anterior depth, μm	370–430
Energy, μJ	1.5	Posterior depth, μm	800–1000
Tang Spot Sep, μm	5	Energy, μJ	2
Rad Spot Sep, μm	5	Angle, degree	90
		Spot Sep, μm	3
		Layer Sep, μm	2

Rad, radial; Sep, separation; Tang, tangential.

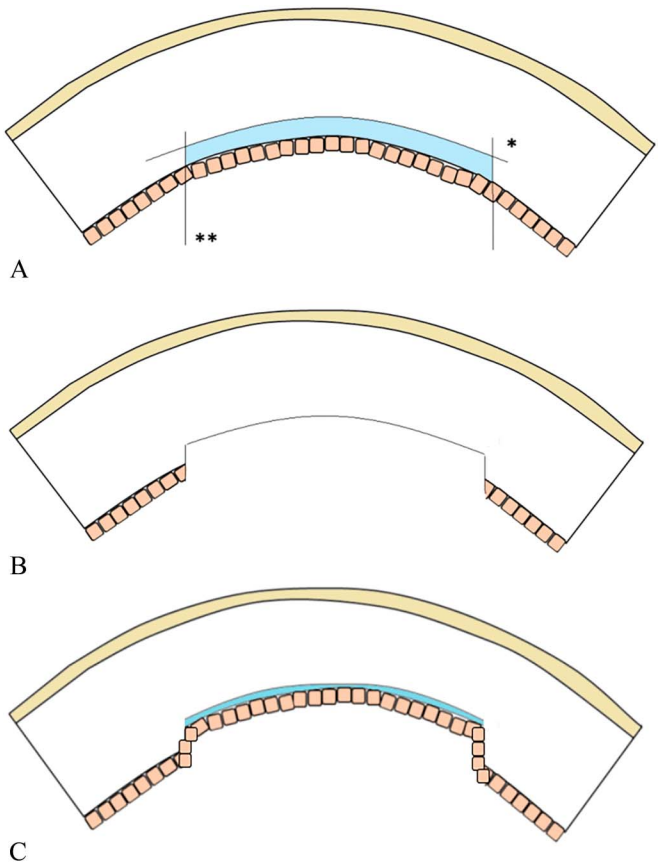

FIGURE 1. Femto-DLEK diagram. A femtosecond laser-assisted posterior intrastromal lamellar cut of 7.5 to 9.0 mm in diameter at 400- to 450-μm depth is performed (A, *), together with an intersecting 90 degree angled posterior side-cut of 7.0- to 8.5-mm of diameter with an anterior depth of 370 to 430 μm and a posterior depth of 800 to 1000 μm (A, **). The dissected posterior recipient disc is removed from the anterior chamber (B), and a 7.0- to 8.5-mm DSAEK or DMEK graft is then inserted (C). Note that in cases in which an ultrathin DSAEK or DMEK graft is used, the anterior chamber depth increases centrally (C).

RESULTS

The 7 consecutive patients treated in the study period had a mean age of 60 years (range: 35–82 years). Indications for surgery, lamellar dissection technique, and visual results are summarized in Table 2.

Indications for surgery were idiopathic posterior corneal copper deposition (non-Wilsons) with incomplete

AU1

TABLE 2. Preoperative (Pre-op), Intraoperative (Intra-op), and Postoperative (Post-op) Data at the Time of Last Follow-up

Patient	Pre-op		Intra-op			Post-op					
No.	DLEK Indication	CDVA, Snellen	Deep Lamellar Cut	Posterior Side-Cut	Donor EK Graft Type	UDVA, Snellen	CDVA, Snellen	Refractive Sphere, D	Refractive Cylinder, D	Refractive Axis, degree	Follow-up, mo
1	Posterior corneal copper deposition	6/9	Femtosecond	Femtosecond	DSAEK	6/6	6/6	0.0	0.0		48
2	Post-DALK	6/18	None	Femtosecond	DSAEK	6/9	6/6	+0.25	−2.50	100	23
3	AC-IOL with failed DSAEK	6/60	Femtosecond	Femtosecond	DSAEK	6/60	6/24	+3.50	−2.0	145	17
4	Post-DALK	1/60	Femtosecond	Femtosecond	DSAEK	6/36	6/18	+2.75	−4.50	100	10
5	AC-IOL with failed DSAEK	6/18	Manual	Femtosecond	DSAEK	6/12	6/9	0.0	−0.75	175	6
6	Post-DALK	1/60	None	Femtosecond	DMEK	6/24	6/9	−0.75	−1.0	100	7
7	Post-DALK	2/60	Femtosecond	Femtosecond	DSAEK	6/36	6/9	−3.0	−9.50	115	23

CDVA, corrected distance visual acuity; D, Diopters; EK, endothelial keratoplasty; UDVA, uncorrected distance visual acuity.

clearance of corneal opacification after conventional DSAEK in the contralateral eye (Fig. 2); failed DSAEK in 2 cases of pseudophakic bullous keratopathy with an anterior chamber intraocular lens (AC-IOL) in situ (Figs. 3A, B); and 4 cases of recipient posterior lamellar failure after DALK (Figs. 3C, D): 1 case in relation with a mild but visually significant residual pre-Descemetic scar, and 3 cases due to a retracted and irregular Descemet membrane and endothelium as a result of a persistent postoperative double anterior chamber that required more than one rebubbling for its resolution. DLEK was performed in the cases of PBK to increase the distance between the retained anterior chamber lenses and the new donor tissue, thereby reducing the risk of repeat failure due to endothelial touch. Deep host tissue lamellar dissection was performed in addition to the posterior side-cut in 2 cases performed for endothelial failure after DALK to excise opacified tissue in the posterior stroma of the DALK donor cornea. In the other 2 post-DALK cases, dissection was limited to a posterior side-cut to remove the damaged host posterior lamella, which was stripped easily from the original graft interface.

One case remained phakic. Three of the 4 remaining non-PBK cases underwent combined phacoemulsification and transplantation procedures with implantation in the capsular bag of an AcrySof SN60WF monofocal intraocular lens implant (Alcon Corp, Fort Worth, TX). All cases of femtolaser lamellar dissection required further manual dissection to free tissue bridges at surgery.

Two eyes, including the single case with a DMEK donor, required rebubbling of the graft for partial detachment 1 week after surgery. All corneas cleared within 6 weeks of surgery and remained optically clear until final follow-up. There were no cases of secondary glaucoma or graft rejection.

Median postoperative follow-up duration was 17 months (range: 6–48 months). Only 2 eyes (patients 3 and 4) failed to reach a spectacle corrected distance visual acuity of 6/9 or better. In both cases, vision was limited by ocular copathology: age-related macular degeneration and irregular astigmatism after DALK (rigid contact lens corrected distance visual acuity = 6/9).

DISCUSSION

This study demonstrates that conventional DSAEK donor preparation and insertion techniques can be combined successfully with femtosecond host tissue dissection in a simplified form of DLEK (Femto-DLEK). Indications include selective removal of pathology involving the posterior corneal stroma, endothelial failure or retained deep scarring after DALK, and revision of failed DSAEK with an enhanced anterior chamber depth in cases of PBK with an AC-IOL.

Femtolaser assistance is particularly useful in facilitating the posterior side-cut in host dissection. The host posterior side-cut was originally achieved with a reverse trephine on a long handle; but this required a large incision. A posterior side-cut can be achieved with custom scissors through a 6-mm pocket entry, or curved vitrectomy scissors through a multipoint entry with surface corneal marking to guide circularity. Dimensional control is poor with these technically difficult alternatives to femtosecond laser dissection, and graft–host overlap or edge gaps may result. Advantages for femtosecond laser dissection include dimensional reproducibility and technical ease; although we did have to divide tissue bridges to complete the side-cut (using curved vitrectomy scissors) in some cases—typically in case in which the incoming laser light path had been shielded by scarring at the site of suture tracks in some of the post-DALK cases.

Tissue bridges were a particular problem for the posterior lamellar cut. It has already been reported that deep stromal femtosecond laser dissections leave a relatively rougher and more irregular interface compared with the more superficial ones, probably in relation with the scattering of the energy and the anatomical differences between the anterior and the less-compacted posterior stromal collagen fibers.[13–15] These occurred prominently beneath old astigmatic scars, but also where there was no obvious overlying anterior stromal opacity other than that associated with corneal edema

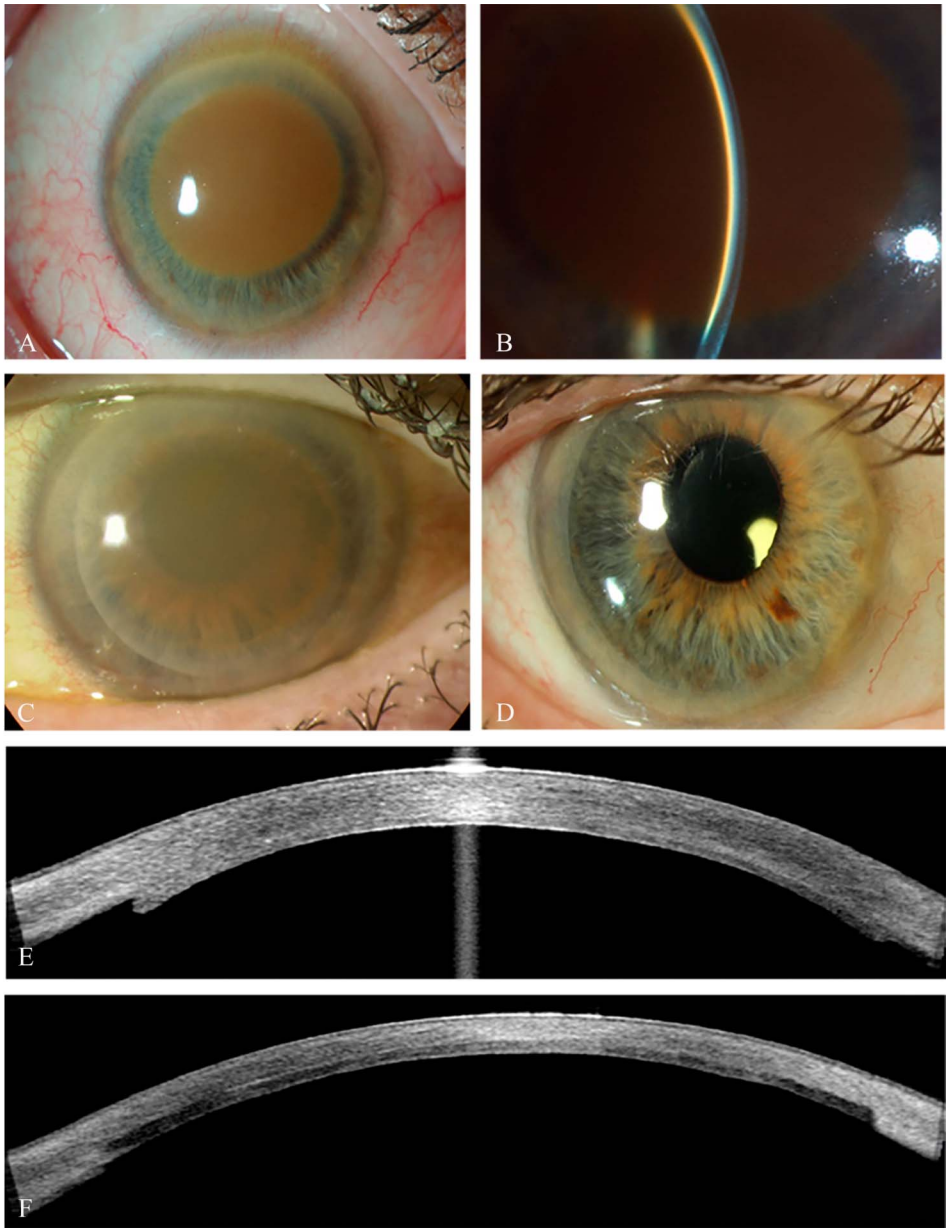

FIGURE 2. Preoperative photographs (A, B) of a patient with symmetrical bilateral deep stromal and Descemet membrane copper deposition secondary to a rare (non-Wilson) copper deposition syndrome. Partial resolution of opacity (C) was achieved with conventional DSAEK (E) in the first eye. Complete restoration of corneal clarity (D) was achieved after Femto-DLEK (F) removing the posterior stroma and Descemet membrane with femtosecond laser-assisted host tissue dissection.

secondary to endothelial failure. Because the posterior side-cut negated the anchoring countertraction required for easy lamellar dissection, tissue bridges were divided using sharp dissection and countertraction with vitrectomy forceps. This maneuver was technically difficult and almost certainly associated with a compromise to host interface smoothness. For this reason, we predissected the last case with manual lamellar dissection at approximately 75% depth 1 week before surgery, and a posterior side-cut only at the time of surgery.

An important future direction will be to explore different permutations of predissection of the host posterior lamella. It may be possible to preserve the dimensional accuracy of a femtolaser cut using a femtolaser lamellar dissection/manual completion/posterior side-cut sequence on the day of surgery. Whatever sequence is used, our recommendation is that the lamellar cut should be confirmed as complete by follow-up manual dissection before the posterior side-cut; unless there is a preexisting interface, as in 2 of our cases of revision of DALK at the host/donor interface in which the host lamella could be removed easily after a posterior side-cut alone. Some technique modifications have already been described to optimize the femtosecond-assisted deep lamellar dissection for DSAEK donor tissue preparation, but this modifications unfortunately cannot be easily applied for DLEK as an intact anterior recipient cornea is required and an endothelial approach for laser recipient stromal dissection is not possible.[13,16] A low-energy laser cut has been found to decrease the interface roughness, but this unlikely will be enough by itself to achieve smooth and reproducible deep lamellar dissections.[17]

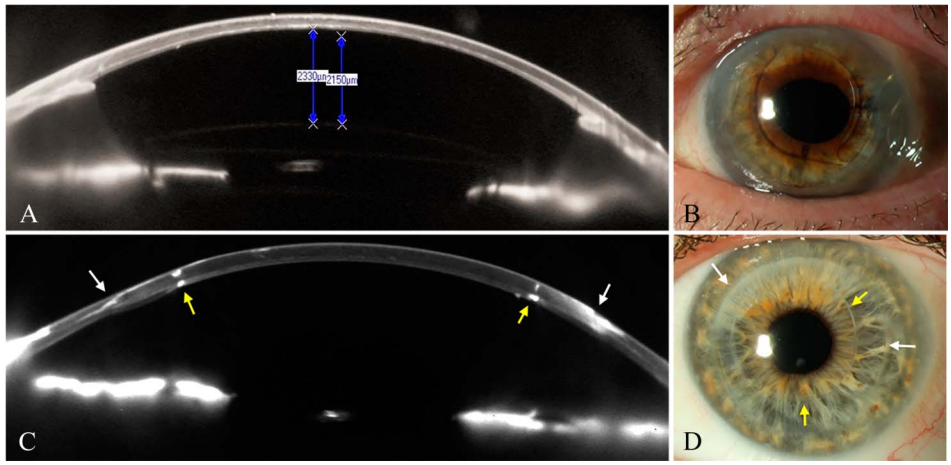

FIGURE 3. Scheimpflug and photographic images: (A, B) Femto-DLEK revision after previously failed DSAEK providing enhanced clearance between the donor endothelium and the anterior chamber lens in a case of pseudophakic bullous keratopathy; and (C, D) showing Femto-DLEK (yellow arrows) revision for retained deep stromal opacity after DALK (white arrows) in a case of postinfective corneal scarring/thinning.

The question of whether to exchange AC-IOLs for suture-fixated posterior chamber IOLs in cases of PBK is unresolved. The goal of exchange for a scleral or iris-fixated posterior chamber IOL (where the existing AC-IOL is stable) is to reduce the risk of optic/endothelial touch. Potential complications of AC-IOL exchange for scleral or iris-fixated posterior chamber IOLs include intraoperative hemorrhage, iris trauma, cyclodialysis, pupil distortion, chronic cystoid macular edema, and late failure of fixation with posterior IOL dislocation.[18,19] A variation of Femto-DLEK in which the donor is countersunk (host posterior lamellar dissection thickness > donor lamellar thickness) to deepen the anterior chamber avoids these complications and may be a valid alternate approach.

AU6 Endothelial cell density (ECD) loss of 43% at 12 months has been reported previously for manual DLEK when compared with preoperative donor cell measurements, whereas for DSAEK and DMEK, ECD loss of 36% has been reported.[20–22] An average manifest refraction astigmatism change of +0.28 ± 1.08 D was observed with manual DLEK, probably in relation with the large scleral incision required for the host posterior corneal excision.[4] DSAEK has been reported to induce a mean hyperopic shift of about +1.5 D, whereas a clinically insignificant hyperopic shift of +0.4 D has been observed after DMEK.[23,24]

AU7 Further larger and prospective studies are necessary to confirm whether Femto-DLEK improves ECD loss better than manual DLEK does and to analyze whether the induced refractive change approximates to the one reported with DSAEK and DMEK.

DLEK is now rarely covered in the endothelial keratoplasty literature, and many corneal surgeons either will never have performed the procedure or will have discarded it because of the technical difficulty and specialized instrumentation required to replicate earlier descriptions of the technique. Our exploratory series shows that femtosecond laser-assisted host dissection, and the posterior side-cut in particular, can be successfully combined with contemporary DSAEK donor preparation and implantation techniques to facilitate surgery for the limited range of indications not covered by DMEK or DSAEK.

REFERENCES

1. Melles GR, Eggink FA, Lander F, et al. A surgical technique for posterior lamellar keratoplasty. *Cornea*. 1998;17:618–626.
2. Terry MA, Ousley PJ. Endothelial replacement without surface corneal incisions or sutures: topography of the deep lamellar endothelial keratoplasty procedure. *Cornea*. 2001;20:14–18.
3. Terry MA. Deep lamellar endothelial keratoplasty (DLEK): pursuing the ideal goals of endothelial replacement. *Eye (Lond)*. 2003;17:982–988.
4. Terry MA, Ousley PJ. Deep lamellar endothelial keratoplasty visual acuity, astigmatism, and endothelial survival in a large prospective series. *Ophthalmology*. 2005;112:1541–1548.
5. Terry MA, Ousley PJ, Will B. A practical femtosecond laser procedure for DLEK endothelial transplantation: cadaver eye histology and topography. *Cornea*. 2005;24:453–459.
6. Lee DH, Chung TY, Chung ES, et al. Case report: femtosecond laser-assisted small incision deep lamellar endothelial keratoplasty. *Korean J Ophthalmol*. 2008;22:43–48.
7. Melles GR, Wijdh RH, Nieuwendaal CP. A technique to excise the descemets' membrane from a recipient cornea (descemetorhexis). *Cornea*. 2004;23:286–288.
8. Price FW Jr, Price MO. Descemet's stripping with endothelial keratoplasty in 50 eyes: a refractive neutral corneal transplant. *J Refract Surg*. 2005;21:339–345.
9. Gorovoy MS. Descemet-stripping automated endothelial keratoplasty. *Cornea*. 2006;25:886–889.
10. Melles GR, Ong TS, Ververs B, et al. Descemet membrane endothelial keratoplasty (DMEK). *Cornea*. 2006;25:987–990.
11. Mian SI, Shtein RM. Femtosecond laser-assisted corneal surgery. *Curr Opin Ophthalmol*. 2007;18:295–299.
12. Rose L, Briceño CA, Stark WJ, et al. Assessment of eye bank-prepared posterior lamellar corneal tissue for endothelial keratoplasty. *Ophthalmology*. 2008;115:279–286.
13. Rousseau A, Bensalem A, Garnier V, et al. Interface quality of endothelial keratoplasty buttons obtained with optimised femtosecond laser settings. *Br J Ophthalmol*. 2012;96:122–127.
14. Vetter JM, Butsch C, Faust M, et al. Irregularity of the posterior corneal surface after curved interface femtosecond laser-assisted versus microkeratome-assisted descemet stripping automated endothelial keratoplasty. *Cornea*. 2012;32:118–124.
15. Phillips PM, Phillips LJ, Saad HA, et al. "Ultrathin" DSAEK tissue prepared with a low-pulse energy, high-frequency femtosecond laser. *Cornea*. 2013;32:81–86.
16. Bernard A, He Z, Gauthier AS, et al. Femtosecond laser cutting of endothelial grafts: comparison of endothelial and epithelial applanation. *Cornea*. 2015;34:209–217.
17. Ziebarth NM, Dias J, Hürmeriç V, et al. Quality of corneal lamellar cuts quantified using atomic force microscopy. *J Cataract Refract Surg*. 2013;39:110–117.

18. Hayashi K, Hirata A, Hayashi H. Possible predisposing factors for in-the-bag and out-of-the-bag intraocular lens dislocation and outcomes of intraocular lens exchange surgery. *Ophthalmology*. 2007;114: 969–975.
19. Gonnermann J, Klamann MK, Maier AK, et al. Visual outcome and complications after posterior iris-claw aphakic intraocular lens implantation. *J Cataract Refract Surg*. 2012;38:2139–2143.
20. Mashor RS, Kaiserman I, Kumar NL, et al. Deep lamellar endothelial keratoplasty: up to 5-year follow-up. *Ophthalmology*. 2010;117: 680–686.
21. Price MO, Gorovoy M, Price FW Jr, et al. Descemet's stripping automated endothelial keratoplasty: three-year graft and endothelial cell survival compared with penetrating keratoplasty. *Ophthalmology*. 2013; 120:246–251.
22. Guerra FP, Anshu A, Price MO, et al. Descemet's membrane endothelial keratoplasty: prospective study of 1-year visual outcomes, graft survival, and endothelial cell loss. *Ophthalmology*. 2011;118:2368–2373.
23. Dupps WJ, Qian Y, Meisler DM. Multivariate model of refractive shift in descemet-stripping automated endothelial keratoplasty. *J Cataract Refract Surg*. 2008;34:578–584.
24. Price MO, Giebel AW, Fairchild KM, et al. Descemet's membrane endothelial keratoplasty: prospective multicentre study of visual and refractive outcomes and endothelial survival. *Ophthalmology*. 2009;116: 2361–2368.