Clinical outcomes of modern lamellar keratoplasty techniques

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Chapter 9

Summary and Conclusions

SUMMARY

After penetrating keratoplasty (PK) had been the preferred method for the treatment of corneal disorders for almost a century, the introduction of advanced lamellar keratoplasty (LK) techniques has changed the field of corneal transplantation substantially over the last two decades.[1,2] These lamellar transplantation techniques provide several advantages over PK: while anterior LK potentially improves graft survival rates by retaining the healthy recipient endothelium,[1,3,4] endothelial keratoplasty (EK) procedures have dramatically enhanced the predictability and speed of visual rehabilitation in the treatment of endothelial disorders, mainly by leaving the anterior corneal surface intact.[1,5,6]

The latest innovation in the field of EK is Descemet membrane endothelial keratoplasty (DMEK), which selectively replaces only the Descemet membrane (DM) and endothelium by donor tissue.[7] The trend towards more selective and minimally invasive transplantation techniques has also led to the development of new treatment options for patients with (advanced) keratoconus,[8-10] including the mid-stromal implantation of an isolated donor Bowman layer (BL), referred to as BL transplantation.[10]

This thesis focusses on the feasibility and clinical outcomes of these two modern LK techniques, i.e. DMEK for managing endothelial disorders (Part I), and BL transplantation for managing advanced keratoconus (Part II).

Part I: Selective, minimal invasive treatment of endothelial disorders

Since its introduction in 1998, EK has evolved from Deep lamellar endothelial keratoplasty (DLEK), to Descemet stripping (automated) endothelial keratoplasty (DSEK/DSAEK) and to DMEK. During this evolution, the technique became more refined, less invasive, increasingly specific, and at the same time the transplanted posterior donor tissue became thinner until it was completely devoid of stromal tissue.[5,6]

This thesis describes that by selectively replacing only diseased corneal layers, DMEK results in a near normal anatomical restoration of the cornea. In our series of the first 300 DMEK eyes, DMEK proved feasible and reproducible, providing rapid visual rehabilitation, with an endothelial cell decline comparable to other EK-techniques, while eliminating the most common complications associated with PK (Chapter 2). Remarkably, DMEK seems to be associated with a lowest risk for allograft rejection (Chapter 2), which has been reported to occur in only 1 to 2.4% of cases after DMEK,[11-13] compared to around 5 to 10% after DSEK/DSAEK (ranging from 0 to 45% in different reports) and 10 to 15% after PK.[14-23] In addition, allograft rejection after DMEK may have a "milder" course, with patients often lacking subjective complaints and showing only minimal objective inflammatory signs on slit-lamp examination.[24,25] Therefore, allograft rejection appears to be manageable with intensified topical steroid treatment in most cases. Interestingly, these reported incidences of allograft rejection after DMEK suggest that the presence of

stromal keratocytes and/or the amount of tissue transplanted may both be important factors to induce the more prominent signs of allograft rejection as known from PK.[12,26] Furthermore, the risk for intra-ocular pressure (IOP) elevation and post-keratoplasty glaucoma after DMEK may be small compared to PK and DSEK/DSAEK, and if occurring, the IOP peaks can often be managed conservatively with topical medication without a significant impact on the visual outcome.[27,28] Pre-existing glaucoma and the application of (higher potent) topical corticosteroids seem to be important risk factors for developing IOP elevation or post-keratoplasty glaucoma after DMEK (Chapter 2).[27,28] In particular phakic eyes undergoing DMEK may be at higher risk to develop air-bubble-induced mechanical angle closure, attributable to an air-bubble (in front of or behind the iris) causing a tilt of the crystalline lens, that closes off the trabecular meshwork.[27,29] The latter may be prevented by reducing the size of the air-bubble at the end of the surgery (after a complete air fill for about one hour) to 20 to 30% of the anterior chamber volume, instead of 50% as is used in pseudophakic eyes.[27,29,30]

The main complication after DMEK remains (partial) graft detachment, appearing in about 10% of our first 300 DMEK cases (Chapter 2), although it has been reported to occur in 60 to 80% of the eyes in some early DMEK cohorts.[31-33] Interestingly, with surgeon's experience, as well as with technique-modifications and -standardization, the percentage of graft dehiscence declined considerably.[34-37] Moreover, not all graft detachments seem clinically significant, i.e. result in incomplete corneal clearance and impaired visual recovery.[35,38] As a rule of thumb, graft detachments of 1/3 or smaller than the graft surface area (not affecting the visual axis) may be considered as not relevant for visual recovery, whereas larger graft detachments are often clinically significant by affecting the visual axis. These larger detachments therefore more frequently require a secondary intervention, such as re-bubbling (repositioning of the graft by filling the recipient anterior chamber with air) or re-transplantation.[13]

Visual rehabilitation after DMEK confirms the hypothesis that thinner grafts may provide superior visual outcomes. In fact, the near normal anatomical restoration of the cornea allows full recovery of an eye's visual potential (Chapter 2). At 1 month after DMEK, about 90% of eyes achieve a spectacle corrected visual acuity of at least 20/40 (0.5), a visual acuity level essential for an independent lifestyle and driving. The final visual acuity level, which is 20/25 (0.8) or better in 75 to 80% of cases, is regularly reached 6 months postoperatively.[37,39,40] This may be in contrast to DSEK/DSAEK, in which the visual acuity has been reported to improve over years,[41,42] with sometimes disappointing initial outcomes.[5,6,21,40] In addition, visual outcomes of 20/17 (1.2) or higher are rarely reported after other EK-techniques, whereas this visual acuity level is achieved in about 10% of eyes after DMEK.[37]

These high visual acuity levels suggest that the optical quality of a post-DMEK cornea may approach the optical quality of a virgin cornea, because in the presence of optical aberrations such visual acuities could reasonably not be achieved. This hypothesis may also be supported by both contrast sensitivity and color vision outcome after DMEK, suggesting an outstanding postoperative visual quality.[43,44] Nevertheless, in a series of 118 DMEK-eyes operated on for Fuchs endothelial dystrophy, anterior and posterior corneal higher order aberrations (HOAs), as well as corneal backscattered light (haze), remained somewhat elevated throughout the first 6 months after DMEK (Chapter 4). This agrees with several reports on haze and abnormal HOAs after DSEK/DSAEK.[45-51] Compared to DSEK/DSAEK however, DMEK-eyes have shown lower degrees of *posterior* corneal aberrations and haze,[52,53] plausibly because a DMEK-graft may better fit the posterior curvature of the host cornea and due to the absence of a stroma-to-stroma interface. The presence of *anterior* corneal HOAs and haze postoperatively may instead depend on the timing of surgical treatment rather than the type of EK-technique employed, since longstanding stromal edema or prolonged decompensation of the host cornea associated with the endothelial disorder may induce irreversible degenerative changes in the anterior stroma.[47-49,54-56]

These HOAs and haze of the *anterior* corneal surface (along with preoperative spectacle corrected distance visual acuity and patient age) have been shown to be important for visual rehabilitation after DMEK (Chapter 4), which is in compliance with the fact that mainly the *anterior* corneal surface is responsible for refracting light. Also, after DSEK/DSAEK, the *anterior* corneal surface may be predominantly responsible for visual recovery,[46,49,57-59] but possibly due to a disruption in parallelism between the anterior and posterior corneal curvature, posterior corneal aberrations may increase rather than decrease whole-eye aberrations and hereby negatively influence visual results.[60] Reasonably, with a thin DMEK-graft, completely devoid of stroma, positioned directly against the host posterior stroma, such an imbalance between anterior and posterior corneal surface may not occur.

Altogether, about 11% of our first 300 DMEK cases presented with incomplete visual recovery (defined as visual acuity outcomes less than 20/25 (0.8)) and/or had visual complaints, such as subtle monocular diplopia or ghost images, related to corneal surface imperfections, whether or not accompanied by (pre-existing) anterior corneal scarring (Chapter 3). In most of these cases, different kinds of contact lenses (i.e. disposable soft silicone hydrogel-, rigid gas permeable- and scleral lenses) proved successful in optimizing vision. The irregularity and lubrication of the anterior corneal surface may be crucial considerations for the choice of contact lens type after DMEK or other EK-techniques (Chapter 3). Importantly, although a post-DMEK cornea may resemble a "virgin" cornea, the altered physiology of the transplanted eye needs to be taken into account when fitting contact lenses, especially in terms of long-term endothelial viability.[13]

An important aspect for good visual rehabilitation after corneal transplantation in general is the predictability of pre- to postoperative refractive changes and stability in corneal power. Conventional PK was notorious for its unpredictable changes in corneal power, high (irregular) astigmatism and/or anisometropia induced by corneal surface incisions and sutures.[61-63] In contrast, EK-procedures induce minimal, more predictable, refractive changes and a more stable corneal power,[64-67] mainly due to the preserved anterior cornea. After DSEK/DSAEK, the shape of the graft (negative lenticular, i.e. thicker at the periphery than in the center), as well as an additional steepening of the posterior corneal curvature caused by the presence of stroma in the donor graft have been suggested to be responsible for a hyperopic change in refraction of about 1 to 1.5 diopters.[68-70] The refractive shift after DMEK may solely be explained by postoperative de-swelling of the recipient's edematous cornea.[67,71,72]

Several DMEK-studies have found a mean hyperopic shift of approximately 0.3 diopters at 3 months after surgery, a more or less stable anterior corneal curvature and a steepening of the posterior corneal curvature of about 1 diopter.[67,71,72] However, large variations in both subjective refractive outcomes and corneal curvature changes (especially the anterior curvature) have been observed by our and other groups (Chapter 2 and 5).[67,71,73] Interestingly, eyes with higher levels of preoperative anterior corneal backscattered light, associated with advanced Fuchs endothelial disease, may be more prone to show pre- to post-DMEK anterior corneal curvature changes (Chapter 5). Also, eyes with partial graft detachments after DMEK, despite of having good corneal clearance and visual rehabilitation, may present anterior corneal curvature variations, possibly owing to more unevenly distributed corneal deturgescence (Chapter 5). Since the changes in posterior corneal curvature and pachymetry after DMEK seem to be generally consistent (Chapter 5), especially these anterior corneal curvature changes may cause the unexpected variations in refractive outcomes. These more variable changes may render IOL-power selection for cataract surgery before or during DMEK more challenging in cases with advanced endothelial disease (Chapter 5).

In conclusion, DMEK provides excellent visual rehabilitation with (partial) graft detachment being the main complication. Since especially the anterior cornea seems to be an important factor for good visual rehabilitation and refractive predictability after DMEK, it may be prudent to avoid long-standing edema and to consider an intervention in a relatively early phase of endothelial disease, before secondary anterior corneal changes may develop. Furthermore, patients with advanced endothelial disease should be counseled about possible inferior spectacle corrected visual outcomes or larger refractive shifts compared to less advanced cases, before commencing DMEK.

Part II: New treatment option for advanced keratoconus

EK has demonstrated that by avoiding corneal surface incisions which are inherent to PK and deep anterior lamellar keratoplasty (DALK), important risks associated with keratoplasty, including suture and wound healing related complications and ocular surface challenges, can be avoided.[1,5,6,26] Moreover, while in EK transplanting the least ´required´ amount of tissue was shown to have the advantage of reducing the risk for allograft rejection,[12,19,26] DALK indicated that graft survival rates may potentially improve by retaining healthy host endothelium.[3,4] Altogether, these findings inspired the development of a new transplantation technique for the treatment of advanced keratoconus, i.e. BL transplantation.

Various options are currently available for the treatment of keratoconus,[10, 74-76] mainly depending on disease severity and visual demands of the patient. Historically, visual rehabilitation was the main objective for treatment, whereas halting keratoconus progression by strengthening the cornea and/or corneal reshaping (possibly improving contact lens tolerance) through respectively UV-crosslinking and intra-corneal ring segments has gained popularity in recent years.[8,9,74-76] However, these new treatment options are currently not advised for eyes with severe thinning and steepening, as in advanced keratoconus.

For eyes with advanced keratoconus, PK and DALK remain the treatments of choice once visual acuity has dropped to unacceptable levels or when contact lenses are no longer tolerated. Although the outcomes of these surgeries may be relatively good for these eyes, the postoperative course is not seldom compromised by a sequence of adverse events.[10,77,78] Especially challenging may be that keratoconus is frequently accompanied by ocular surface and atopic disorders.[79-85] Actually, increased levels of inflammatory molecules have recently been found in the tear film of keratoconic eyes relating to disease severity.[85-88] This finding supports the recent hypothesis that the pathophysiological mechanism of keratoconus may (partly) be caused by longstanding chronic inflammation,[82,83,86,87] which should be taken into consideration when deciding to perform PK or DALK in these cases. Another reason to avoid or postpone PK/DALK for as long as possible is the young age of the average keratoconus patient, which possibly necessitates re-transplantation later in life due to the usually shorter life expectancy of the graft in contrast to the patient.

Hence, in chapter 6, a new surgical approach for the treatment of advanced keratoconus, i.e. BL transplantation, is described. The treatment was designed to enable long-term stability of advanced keratoconus corneas that were not eligible for either UV-crosslinking or intra-corneal ring segments. An important motive to develop this new treatment was the clinical observation that many advanced keratoconus patients, who had been referred to our clinic for corneal transplantation due to poor vision or contact lens intolerance, could still be satisfactory facilitated with a proper contact lens fit. In fact, many new improvements in contact lens designs, including hybrid-, rigid gas permeable- and scleral-lenses,[89,90] aid in delaying the need for corneal transplantation, also in eyes with severe keratoconus. If so, eyes no longer eligible for either UV-crosslinking or intracorneal ring segments,[91-93] but still being adequately correctable with contact lenses, would similarly benefit from halting further keratoconus progression to potentially avoid a PK or DALK.

Because keratoconus corneas invariably show fragmentation of the BL,[94] we hypothesized that the possible functionality of the BL in stabilizing the cornea could be restored through implantation of an isolated BL (Chapter 6). At the same time, the firmness of such a BL-graft,[95-97] and a wound-healing response between the host stroma and the BL-graft could enable stabilization of the ectasia,[98,99] with a negligible risk of allograft rejection because of the acellular nature of a BL.

BL-grafts were isolated from donor corneas not suitable for PK or EK or from anterior donor-lamellae remaining after previous DMEK-graft preparation, allowing efficient use of donor tissue.[100] The surgery itself was performed by manually dissecting a mid-stromal pocket over 360° up to the limbus within the recipient cornea, using the Melles manual DALK-technique,[101,102] after which the isolated BL-graft was inserted into the created pocket via a glide, unrolled and stretched out to the corneal periphery. The position of the BL-graft was purposely chosen at mid-stromal depth to be able to fixate the graft without the need for sutures and to avoid corneal surface concessions (Chapter 6).

The clinical evaluation of the first case series of 22 progressive advanced keratoconus eyes with a mean follow-up of 21 months after BL transplantation showed promising outcomes (Chapter 7). The only complication encountered was an intraoperative DM perforation during the dissection in two eyes. The cornea of one of these two eyes cleared slowly and vision improved within the first months after surgery. The other eye underwent PK for progressive corneal decompensation. In the other 20 eyes, flattening of the corneal curvature of approximately 8 diopters on average was observed in the first postoperative months, with the largest corneal flattening obtained in more advanced cases, with more central cones (Chapter 7). The flattening of the cornea was accompanied by an improvement in spectacle-corrected visual acuity and a decrease in corneal HOAs (especially spherical aberration).[103] Contact lens-corrected visual acuity showed no changes from before to after BL transplantation, which indicates that potential candidates for this treatment should present with an acceptable vision with their lenses.

A disadvantage of positioning a BL-graft in the mid-stroma of a host cornea may be some increase in corneal backscatter,[103] which was found up to 5 years after BL transplantation (Chapter 8). The elevation is possibly initiated by interface irregularities and/or differences in refractive indices between the BL-graft and host stroma. Nevertheless, the clinical impact of this rise in corneal densitometry may be minimal given the objective and subjective lack of visual disturbance. After the initial improvement in spectacle-corrected visual acuity in the first year after BL transplantation, no further changes in vision were found up to now 5 years postoperatively (Chapter 8). The only postoperative complication observed in this period was a corneal hydrops at 4½ years postoperatively in the eye of a 33-year old male patient with a history of eye rubbing and seasonal allergies (Chapter 8). Overall, BL transplantation was estimated to be successful, i.e. keratoconus disease progression was avoided in 83% of operated eyes at around 50 months postoperatively (Chapter 8), an encouraging result for this generally challenging patient group (advanced corneal ectasia with severe corneal thinning, corneal scarring, atopy and corneal surface disease).

To summarize, BL transplantation aims at corneal stabilization in eyes with advanced keratoconus to enable continued contact lens wear for visual functionality. The treatment seems a promising supplementary option in the management of advanced keratoconus in order to postpone PK/DALK, while minimizing the risk of (long-term) complications. Longer follow-up and larger studies will provide further insight in the potential benefits of this new treatment option.

Overall remarks

Whereas in the past mainly one type of corneal transplantation, i.e. PK, was performed for all different indications, nowadays there are numerous options per indication. Both endothelial disorders and keratoconus are currently treated with minimally invasive, targeted surgeries, away from full thickness corneal replacement, allowing earlier intervention, fewer postoperative complications, and several years of useful vision. Since both spectacle- and contact lens correction are fundamental aspects of postoperative visual rehabilitation, good collaboration between the different eye care practitioners, i.e. ophthalmologists, corneal surgeons, optometrists and opticians, remains essential to provide the patient with the best postoperative care.

REFERENCES

1. Tan DT, Dart JK, Holland EJ, Kinoshita S. Corneal transplantation. Lancet. 2012;379:1749-1761
2. Eye Bank Association of America. 2015 Eye Banking Statistical Report. Washington, D.C., United States, 2016. Available at http://restoresight.org/wp-content/uploads/2016/03/2015-Statistical-Report.pdf
3. Borderie VM, Guilbert E, Touzeau O, Laroche L. Graft rejection and graft failure after anterior lamellar versus penetrating keratoplasty. Am J Ophthalmol 2011;151:1024-1029
4. Reinhart WJ, Musch DC, Jacobs DS, et al. Deep anterior lamellar keratoplasty as an alternative to penetrating keratoplasty: a report by American Academy of Ophthalmology. Ophthalmology 2011;118:209-218
5. Melles GR. Posterior lamellar keratoplasty: DLEK to DSEK to DMEK. Cornea 2006;25:879-881
6. Price MO, Price FW Jr. Endothelial keratoplasty - a review. Clin Experiment Ophthalmol 2010;38:128-140
7. Melles GR, Ong TS, Ververs B, van der Wees J. Descemet membrane endothelial keratoplasty (DMEK). Cornea 2006;25:987-990
8. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-ainduced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol 2003;135:620-627
9. Pinero DP, Alio JL. Intracorneal ring segments in ectatic corneal disease: A review. Clin Experiment Ophthalmol 2010;38:154-167
10. Parker JS, van Dijk K, Melles GR. Treatment options for advanced keratoconus: A review. Surv Ophthalmol 2015;60:459-480
11. Dapena I, Ham L, Netukova M, et al. Incidence of early allograft rejection after Descemet membrane endothelial keratoplasty. Cornea 2011;30:1341-1345
12. Anshu A, Price MO, Price F Jr. Risk of corneal transplant rejection significantly reduced with Descemet's membrane endothelial keratoplasty. Ophthalmology 2012;119:536-540
13. Ham L, Dapena I, Liarakos VS, et al. Midterm Results of Descemet Membrane Endothelial Keratoplasty: 4 to 7 Years Clinical Outcome. Am J Ophthalmol 2016;171:113-121
14. Price MO, Jordon CS, Moore G, Price FW Jr. Graft rejection episodes after Descemet stripping with endothelial keratoplasty: Part two: the statistical analysis of probability and risk factors. Br J Ophthalmol 2009;93:391-395
15. Thompson RW Jr, Price MO, Bowers PJ, Price FW Jr. Long-term graft survival after penetrating keratoplasty. Ophthalmology 2003;110:1396-1402
16. Williams KA, Lowe MT, Keane MC, et al. The Australian corneal graft registry. Adelaide, Snap Printing, 2012 report
17. Claesson M, Armitage WJ. Ten-year follow-up of graft survival and visual outcome after penetrating keratoplasty in Sweden. Cornea 2009;28:1124-1129
18. Küchle M, Cursiefen C, Nguyen NX, et al. Risk factors for corneal allograft rejection: intermediate results of a prospective normal-risk keratoplasty study. Graefes Arch Clin Exp Ophthalmol 2002;240:580-584
19. Allan BDS, Terry MA, Price FW Jr, et al. Corneal transplant rejection rate and severity after endothelial keratoplasty. Cornea 2007;26:1039-1042
20. Jordan CS, Price MO, Trespalacios R, et al. Graft rejection episodes after Descemet stripping with endothelial keratoplasty: part one: clinical signs and symptoms. Br J Ophthalmol 2009;93:387-390

21. Lee WB, Jacobs DS, Musch DC, et al. Descemet's stripping endothelial keratoplasty: safety and outcomes: a report by the American Academy of Ophthalmology. Ophthalmology 2009;116:1818-1830
22. Wu EI, Ritterband DC, Yu G, et al. Graft rejection following Descemet stripping automated endothelial keratoplasty: features, risk factors, and outcomes. Am J Ophthalmol 2012;153:949-957
23. Li JY, Terry MA, Goshe J, et al. Graft rejection after Descemet's stripping automated endothelial keratoplasty: graft survival and endothelial cell loss. Ophthalmology 2012;119:90-94
24. Baydoun L, Livny E, Ham L, et al. 360-Degree Scheimpflug Imaging to Predict Allograft Rejection After Descemet Membrane Endothelial Keratoplasty. Cornea 2016;35:1385-1390
25. Price MO, Scanameo A, Feng MT, et al. Descemet's membrane endothelial keratoplasty: risk of immunologic rejection episodes after discontinuing topical corticosteroids. Ophthalmology 2016;123:1232-1236
26. Price FW Jr, Feng MT, Price MO. Evolution of Endothelial Keratoplasty: Where Are We Headed? Cornea 2015;34:S41-47
27. Naveiras M, Dirisamer M, Parker J, et al. Causes of glaucoma after descemet membrane endothelial keratoplasty. Am J Ophthalmol 2012;153:958-966
28. Maier AK, Wolf T, Gundlach E, et al. Intraocular pressure elevation and post-DMEK glaucoma following Descemet membrane endothelial keratoplasty. Graefes Arch Clin Exp Ophthalmol 2014;252:1947-1954
29. Parker J, Dirisamer M, Naveiras M, et al. Outcomes of Descemet membrane endothelial keratoplasty in phakic eyes. J Cataract Refract Surg 2012;38:871-877
30. Dapena I, Moutsouris K, Droutsas K, et al. Standardized "no-touch" technique for Descemet membrane endothelial keratoplasty. Arch Ophthalmol 2011;129:88-94
31. Price MO, Giebel AW, Fairchild KM, Price FW Jr. Descemet's membrane endothelial keratoplasty: prospective multicenter study of visual and refractive outcomes and endothelial survival. Ophthalmology 2009;116:2361-2368
32. Laaser K, Bachmann BO, Horn FK, et al. Descemet membrane endothelial keratoplasty combined with phacoemulsification and intraocular lens implantation: advanced triple procedure. Am J Ophthalmol 2012;154:47-55
33. 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
34. Dapena I, Ham L, Droutsas K, et al. Learning Curve in Descemet's Membrane Endothelial Keratoplasty: First Series of 135 Consecutive Cases. Ophthalmology 2011;118:2147-2154
35. Dirisamer M, van Dijk K, Dapena I, et al. Prevention and management of graft detachment in descemet membrane endothelial keratoplasty. Arch Ophthalmol 2012;130:280-291
36. Kruse FE, Schrehardt US, Tourtas T. Optimizing outcomes with Descemet's membrane endothelial keratoplasty. Curr Opin Ophthalmol 2014;25:325-334
37. Rodríguez-Calvo-de-Mora M, Quilendrino R, Ham L, et al. Clinical outcome of 500 consecutive cases undergoing Descemet's membrane endothelial keratoplasty. Ophthalmology 2015;122:464-470
38. Dirisamer M, Dapena I, Ham L, et al. Patterns of corneal endothelialization and corneal clearance after descemet membrane endothelial keratoplasty for fuchs endothelial dystrophy. Am J Ophthalmol 2011;152:543-555
39. Ham L, Balachandran C, Verschoor CA, et al. Visual rehabilitation rate after isolated Descemet membrane transplantation: Descemet membrane endothelial keratoplasty. Arch Ophthalmol 2009;127:252-255

40. Tourtas T, Laaser K, Bachmann BO, et al. Descemet membrane endothelial keratoplasty versus Descemet stripping automated endothelial keratoplasty. Am J Ophthalmol 2012;153:1082-1090
41. Li JY, Terry MA, Goshe J, et al. Three year visual acuity outcomes after Descemet's stripping automated endothelial keratoplasty. Ophthalmology 2012;119:1126-1129
42. Wacker K, Baratz KH, Maguire LJ, et al. Descemet stripping endothelial keratoplasty for Fuchs' endothelial corneal dystrophy: five-year results of a prospective study. Ophthalmology 2016;123:154-160
43. Cabrerizo J, Livny E, Musa FU,et al. Changes in color vision and contrast sensitivity after descemet membrane endothelial keratoplasty for fuchs endothelial dystrophy. Cornea 2014;33:1010-1015
44. Price DA, Price MO, Lopez A, Price FW Jr. Effect of Descemet Membrane Endothelial Keratoplasty on Color Vision in Patients With Fuchs Dystrophy. Cornea 2016;35:1045-1048
45. Koh S, Maeda N, Nakagawa T, et al. Characteristic higherorder aberrations of the anterior and posterior corneal surfaces in 3 corneal transplantation techniques. Am J Ophthalmol 2012;153:284-290
46. Patel SV, Baratz KH, Maguire LJ, et al. Anterior corneal aberrations after Descemet's stripping endothelial keratoplasty for Fuchs' endothelial dystrophy. Ophthalmology 2012;119:1522-1529
47. Patel SV, Baratz KH, Hodge DO, et al. The effect of corneal light scatter on vision after Descemet stripping with endothelial keratoplasty. Arch Ophthalmol 2009;127:153-160
48. Morishige N, Yamada N, Teranishi S, et al. Detection of subepithelial fibrosis associated with corneal stromal edema by second harmonic generation imaging microscopy. Invest Ophthalmol Vis Sci 2009;50:3145-3150
49. Morishige N, Chikama T, Yamada N, et al. Effect of preoperative duration of stromal edema in bullous keratopathy on early visual acuity after endothelial keratoplasty. J Cataract Refract Surg 2012;38:303-308
50. Alomar TS, Al-Aqaba M, Gray T, et al. Histological and confocal microscopy changes in chronic corneal edema: implications for endothelial transplantation. Invest Ophthalmol Vis Sci 2011;52:8193-8207
51. Baratz KH, McLaren JW, Maguire LJ, Patel SV. Corneal haze determined by confocal microscopy 2 years after Descemet stripping with endothelial keratoplasty for Fuchs corneal dystrophy. Arch Ophthalmol 2012;130:867-874
52. Rudolph M, Laaser K, Bachmann BO, et al. Corneal higher-order aberrations after Descemet's membrane endothelial keratoplasty. Ophthalmolog 2012;119:528-535
53. Dirisamer M, Parker J, Naveiras M, et al. Identifying causes for poor visual outcome after DSEK/DSAEK following secondary DMEK in the same eye. Acta Ophthalmol 2013;91:131-139
54. Chamberlain W, Omid N, Lin A, et al. Comparison of corneal surface higher-order aberrations after endothelial keratoplasty, femtosecond laser-assisted keratoplasty, and conventional penetrating keratoplasty. Cornea 2012;31:6-13
55. Elhalis H, Azizi B, Jurkunas UV. Fuchs endothelial corneal dystrophy. Ocul Surf 2010;8:173-184
56. Baydoun L, van Dijk K, Dapena I, et al. Repeat Descemet membrane endothelial keratoplasty after complicated primary Descemet membrane endothelial keratoplasty. Ophthalmology 2015;122:8-16
57. Muftuoglu O, Prasher P, Bowman RW, et al. Corneal higher-order aberrations after Descemet's stripping automated endothelial keratoplasty. Ophthalmology 2010;117:878-884
58. Yamaguchi T, Negishi K, Yamaguchi K, et al. Effect of anterior and posterior corneal surface irregularity on vision after Descemet stripping endothelial keratoplasty. J Cataract Refract Surg 2009;35:688-694

59. McLaren JW, Patel SV. Modeling the effect of forward scatter and aberrations on visual acuity after endothelial keratoplasty. Invest Ophthalmol Vis Sci 2012;53:5545-5551
60. Yamaguchi T, Ohnuma K, Tomida D, et al. The contribution of the posterior surface to the corneal aberrations in eyes after keratoplasty. Invest Ophthalmol Vis Sci 2011;52:6222-6229
61. Frost NA, Wu J, Lai TF, Coster DJ. A review of randomized controlled trials of penetrating keratoplasty techniques. Ophthalmology 2006;113:942-949
62. Binder PS. The triple procedure; refractive results. 1985 update. Ophthalmology 1986; 93:1482-1488
63. Claesson M, Armitage WJ. Ten-year follow-up of graft survival and visual outcome after penetrating keratoplasty in Sweden. Cornea 2009;28:1124-1129
64. Terry MA, Ousley PJ. In pursuit of emmetropia: spherical equivalent refraction results with deep lamellar endothelial keratoplasty (DLEK). Cornea 2003;22:619-626
65. Bahar I, Kaiserman I, McAllum P, et al. Comparison of posterior lamellar keratoplasty techniques to penetrating keratoplasty. Ophthalmology 2008;115:1525-1533
66. 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
67. Ham L, Dapena I, Moutsouris K, et al. Refractive change and stability after Descemet membrane endothelial keratoplasty Effect of corneal dehydration-induced hyperopic shift on intraocular lens power calculation. J Cataract Refract Surg 2011;37:1455-1464
68. 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
69. Holtz HA, Meyer JJ, Espandar L, et al. Corneal profile analysis after Descemet stripping automated endothelial keratoplasty and its relationship to postoperative hyperopic shift. J Cataract Refract Surg 2008;34:211-214
70. Rao SK, Leung CKS, Cheung CYL, et al. Descemet stripping endothelial keratoplasty: effect of the surgical procedure on corneal optics. Am J Ophthalmol 2008;145:991-996
71. Schoenberg ED, Price FW Jr, Miller J, et al. Refractive outcomes of Descemet membrane endothelial keratoplasty triple procedures (combined with cataract surgery). J Cataract Refract Surg 2015;41:1182-1189
72. Droutsas K, Lazaridis A, Papaconstantinou D, et al. Visual outcomes after descemet membrane endothelial keratoplasty versus Descemet stripping automated endothelial keratoplasty-comparison of specific matched pairs. Cornea 2016;35:765-771
73. Alnawaiseh M, Rosentreter A, Eter N, Zumhagen L. Changes in Corneal Refractive Power for Patients With Fuchs Endothelial Dystrophy After DMEK. Cornea 2016;35:1073-1077
74. McGhee CN, Kim BZ, Wilson PJ. Contemporary Treatment Paradigms in Keratoconus. Cornea 2015;34:S16-23
75. Mandathara PS, Stapleton FJ, Willcox MD. Outcome of Keratoconus Management: Review of the Past 20 Years' Contemporary Treatment Modalities. Eye Contact Lens 2017;43:141-154
76. Jhanji V, Sharma N, Vajpayee RB. Management of keratoconus: current scenario. Br J Ophthalmol 2011;95:1044-1050
77. Olson R, Pingree M, Ridges R, et al. Penetrating keratoplasty for keratoconus: a longterm review of results and complications. J Cataract Refract Surg 2000;26:987-991
78. Christo C, van Rooij J, Geerards A, et al. Suture-related complications following keratoplasty: a 5-year retrospective study. Cornea 2001;20:816-819
79. Rahi A, Davies P, Ruben M, et al. Keratoconus and coexisting atopic disease. Br J Ophthalmol 1977;61:761-764

80. Yildiz EH, Erdurmus M, Hammersmith KM, et al. Comparative study of graft rejection in keratoconus patients with and without self-reported atopy. Cornea. 2009;28:846-850
81. Sugar J, Macsai MS. What causes keratoconus? Cornea 2012;31:716-719
82. Lema I, Sobrino T, Durán JA, et al. Subclinincal keratoconus and inflammatory molecules from tears. Br J Ophthalmol 2009;6:820-824
83. McMonnies CW. Inflammation and keratoconus. Optom Vis Sci 2015;92:35-41
84. Dienes L, Kiss HJ, Perényi K, et al. Corneal sensitivity and dry eye symptoms in patients with keratoconus. PLoS One 2015;10:e0141621
85. Wisse RP, Kuiper JJ, Gans R, et al. Cytokine Expression in Keratoconus and its Corneal Microenvironment: A Systematic Review. Ocul Surf 2015;13:272-283
86. Lema I, Durán JA. Inflammatory molecules in the tears of patients with keratoconus. Ophthalmology 2005;112:654-659
87. Galvis V, Sherwin T, Tello A, et al. Keratoconus: an inflammatory disorder? Eye (Lond) 2015;29:843-859
88. Kolozsvari BL, Petrovski G, Gogolak P, et al. Association between mediators in the tear fluid and the severity of keratoconus. Ophthalmic Res 2014;51:46-51
89. Visser ES, Wisse RP, Soeters N, et al. Objective and subjective evaluation of the performance of medical contact lenses fitted using a contact lens selection algorithm. Cont Lens Anterior Eye 2016;39:298-306
90. Jeng BH, Farid M, Patel SV, Schwab IR. Corneal Cross-linking for Keratoconus: A Look at the Data, the Food and Drug Administration, and the Future. Ophthalmology 2016;123:2270-2272
91. Hafezi F. Limitation of collagen cross-linking with hypoosmolar riboflavin solution: failure in an extremely thin cornea. Cornea 2011;30:917-919
92. Health Quality Ontario. Intrastromal corneal ring implants for corneal thinning disorders: an evidence-based analysis. Ont Health Technol Assess Ser 2009;9:1-90.
93. Koller T, Mrochen M, Seiler T. Complication and failure rates after corneal crosslinking. J Cataract Refract Surg 2009;35:1358-1362
94. Ambekar R, Toussaint KC Jr, Johnson AW. The effect of keratoconus on the structural, mechanical, and optical properties of the cornea. J Mech Behav Biomed Mater 2011;4:223-236
95. Marshall J. The 2014 Bowman Lecture-Bowman's and Bruch's: a tale of two membranes during the laser revolution. Eye (Lond) 2015;29:46-64
96. Wilson SE, Hong JW. Bowman's layer structure and function: critical or dispensable to corneal function? A hypothesis. Cornea 2000;19:417-420
97. Abahussin M, Hayes S, Knox Cartwright NE, et al. 3D collagen orientation study of the human cornea using X-ray diffraction and femtosecond laser technology. Invest Ophthalmol Vis Sci 2009;50:5159-5164
98. Melles GRJ, Binder PS. A comparison of wound healing in sutured and unsutured corneal wounds. Arch Ophthalmol 1990;108:1460-1469
99. Melles GRJ, Binder PS, Anderson JA. Variation in healing throughout the depth of long-term, unsutured, corneal wounds in human autopsy specimens and monkeys. Arch Ophthalmol 1994;112:100-109
100. Groeneveld-van Beek EA, Parker J, Lie JT, et al. Donor Tissue Preparation for Bowman Layer Transplantation. Cornea 2016;35:1499-1502
101. Melles GR, Lander F, Rietveld FJ, et al. A new surgical technique for deep stromal, anterior lamellar keratoplasty. Br J Ophthalmol 1999;83:327-333

102. Melles GR, Rietveld FJ, Beekhuis WH, Binder PS. A technique to visualize corneal incision and lamellar dissection depth during surgery. Cornea 1999;18:80-86

103. Luceri S, Parker J, Dapena I, et al. Corneal Densitometry and Higher Order Aberrations After Bowman Layer Transplantation: 1-Year Results. Cornea 2016;35:959-966