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## Clinical outcomes of modern lamellar keratoplasty techniques

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# Chapter 9

## Summary and Conclusions

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## 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.<sup>1,2</sup> These lamellar transplantation techniques provide several advantages over PK: while anterior LK potentially improves graft survival rates by retaining the healthy recipient endothelium,<sup>1,3,4</sup> 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.<sup>1,5,6</sup>

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.<sup>7</sup> 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,<sup>8-10</sup> including the mid-stromal implantation of an isolated donor Bowman layer (BL), referred to as BL transplantation.<sup>10</sup>

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.<sup>5,6</sup>

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,<sup>11-13</sup> compared to around 5 to 10% after DSEK/DSAEK (ranging from 0 to 45% in different reports) and 10 to 15% after PK.<sup>14-23</sup> 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.<sup>24,25</sup> 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.<sup>12,26</sup> 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.<sup>27,28</sup> 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).<sup>27,28</sup> 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.<sup>27,29</sup> 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.<sup>27,29,30</sup>

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.<sup>31-33</sup> Interestingly, with surgeon's experience, as well as with technique-modifications and -standardization, the percentage of graft dehiscence declined considerably.<sup>34-37</sup> Moreover, not all graft detachments seem clinically significant, i.e. result in incomplete corneal clearance and impaired visual recovery.<sup>35,38</sup> 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.<sup>13</sup>

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.<sup>37,39,40</sup> This may be in contrast to DSEK/DSAEK, in which the visual acuity has been reported to improve over years,<sup>41,42</sup> with sometimes disappointing initial outcomes.<sup>5,6,21,40</sup> 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.<sup>37</sup>

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 as 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.<sup>43,44</sup> 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.<sup>45-51</sup> Compared to DSEK/DSAEK however, DMEK-eyes have shown lower degrees of *posterior* corneal aberrations and haze,<sup>52,53</sup> 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.<sup>47-49,54-56</sup>

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,<sup>46,49,57-59</sup> 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.<sup>60</sup> 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.<sup>13</sup>

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.<sup>61-63</sup> In contrast, EK-procedures induce minimal, more predictable, refractive changes and a more stable corneal power,<sup>64-67</sup> 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.<sup>68-70</sup> The refractive shift after DMEK may solely be explained by postoperative de-swelling of the recipient's edematous cornea.<sup>67,71,72</sup>

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.<sup>67,71,72</sup> 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).<sup>67,71,73</sup> Interestingly, eyes with higher levels of preoperative anterior corneal back-scattered 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.<sup>1,5,6,26</sup> Moreover, while in EK transplanting the least 'required' amount of tissue was shown to have the advantage of reducing the risk for allograft rejection,<sup>12,19,26</sup> DALK indicated that graft survival rates may potentially improve by retaining healthy host endothelium.<sup>3,4</sup> 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,<sup>10,74-76</sup> 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.<sup>8,9,74-76</sup> 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.<sup>10,77,78</sup> Especially challenging may be that keratoconus is frequently accompanied by ocular surface and atopic disorders.<sup>79-85</sup> Actually, increased levels of inflammatory molecules have recently been found in the tear film of keratoconic eyes relating to disease severity.<sup>85-88</sup> This finding supports the recent hypothesis that the pathophysiological mechanism of keratoconus may (partly) be caused by longstanding chronic inflammation,<sup>82,83,86,87</sup> 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 satisfactorily facilitated with a proper contact lens fit. In fact, many new improvements in contact lens designs, including hybrid-, rigid gas permeable- and scleral-lenses,<sup>89,90</sup> 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,<sup>91-93</sup> 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,<sup>94</sup> 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,<sup>95-97</sup> and a wound-healing response between the host stroma and the BL-graft could enable stabilization of the ectasia,<sup>98,99</sup> 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.<sup>100</sup> 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,<sup>101,102</sup> 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).<sup>103</sup> 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,<sup>103</sup> 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.

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