Descemet membrane endothelial keratoplasty: graft rejection, failure and survival

Baydoun, L.

CHAPTER 10

Summary, Discussion and Future Directions

SUMMARY AND DISCUSSION

Endothelial Keratoplasty (EK) emerged almost 25 years ago, namely in 1998, and heralded a new era in the field of corneal transplantation.[1-4] Until then, its predecessor, Penetrating Keratoplasty (PK) had been the backbone of any corneal layer replacement for almost 100 years.[5] Within less than a decade, various minimally-invasive EK techniques have been introduced for patients with corneal endothelial disease. A rapid transition from Deep Lamellar Endothelial Keratoplasty (DLEK) to Descemet Stripping (automated) Endothelial Keratoplasty (DS(A)EK) to Descemet Membrane Endothelial Keratoplasty (DMEK) occurred.[6] With each technical refinement, the transplanted graft became thinner and at the same time uncertainty grew concerning endothelial cell density (ECD) decrease and survival due to the more challenging intraoperative graft handling, especially in DMEK.[7] Another concern was the more frequent and seemingly inevitable postoperative graft dehiscence that necessitated repeat intervention in certain cases.[8-11] Despite all these doubts, DMEK has proven to be the culmination of technique `fine-tuning´ as the nearly complete anatomical restoration provided quick postoperative functional `perfection´.[12-17] Another advantage of the thin DMEK graft may contribute to the reduced risk and milder forms of immunologic reactions.[18] The latter could be further reduced by transplanting smaller grafts as in novel modified tissue-sparing DMEK techniques, such as Quarter-DMEK.[19]

This thesis evaluated graft survival and reasons for repeat surgery after primary DMEK and the clinical outcome after repeat DMEK. In addition, diagnostic methods to predict allograft rejection and the feasibility of transplanting multiple Quarter-DMEK grafts from the same donor, that potentially carry a reduced antigen load, were investigated.

DMEK graft survival and repeat DMEK for graft `failure´

DMEK survival: Pioneering in the 21st century

The first in vivo DMEK surgery was performed in 2006 on a Dutch male with Fuchs Endothelial Corneal Dystrophy (FECD).[20] Owing to the outstanding early clinical outcomes that have consistently been confirmed in numerous studies from different transplant centers, this technique has risen worldwide to a popular standard procedure in the treatment of corneal endothelial disorders.[21-23] The initial case report of the first surgery in 2006 showed fast and complete visual recovery within only one week.[20] The same patient underwent DMEK in his contralateral eye 10 months later. Regular follow-up visits enabled us to report the clinical

evolution until 9 and 10 years postoperatively in his right and left eye, respectively (**Chapter 2**).[24] The corneas were clear, lacking signs of endothelial dysfunction or immunologic reaction. For both eyes, we noted excellent long-term outcomes regarding best-corrected visual acuity (BCVA), ECD and lack of complications. This first patient unifies all DMEK advantages, such as rapid visual recovery, sustainable outcomes with superlative patient satisfaction, and graft longevity.

The increasing number of DMEK surgeries at our institute laid the foundation for the first long-term study on graft and endothelial survival in a series of the first 500 DMEK cases (**Chapter 3**).[25] A subgroup analysis was applied to assess an association with surgical indication (FECD versus bullous keratopathy BK), and graft adherence (attached versus partially detached). The results in this large cohort confirmed the outcomes of the first DMEK patient in terms of ECD decay and graft survival up to 8 years after DMEK. In addition, higher ECDs were found in FECD than in BK eyes and in attached compared to partially detached grafts. Likewise, survival probabilities were better in FECD than in BK eyes (97% versus 84%) with the same trend for eyes with attached versus partially detached grafts (97% versus 91%). Graft failure occurred in only 3 % of eyes and was attributed either to the pioneer´s learning curve, concomitant ocular pathologies (e.g., glaucoma) or complications (e.g., allograft rejection, low ECD in the presence of graft detachment). More than 50% of the failures were noted within the first year. Seemingly, only eyes with comorbidities or complications experienced timely graft failure. Hence, this study demonstrated an excellent prognosis on DMEK graft longevity, especially in eyes with FECD that had an attached graft and no concurrent ocular disease or early postoperative DMEK complication.

The survival study triggered a viewpoint on refining the term ´graft failure` in EK outcome reports (**Chapter 4**).[26] To assess donor endothelial viability in DMEK, it appears essential to identify the cause of corneal edema that besides irrevocable endothelial dysfunction may originate from major/complete graft detachment or false (inverted) graft positioning. The latter two should not be misnamed as ´graft failures´ but rather titled as technical failures because corneal edema often resolves after proper graft re-positioning and re-orientation, which proves the presence of viable donor endothelium.[27] Likewise, cases that showed ´spontaneous corneal clearance´ despite major/complete DMEK detachment,[28] will also not reflect donor endothelial viability, since the detected endothelium across the bare stroma may have derived from endothelial cell migration of the donor and/or recipient that both could have an impaired long-term survival compared to donor endothelial cells on an attached DMEK graft. Consequently, accurate

characterization and inclusion criteria with regard to the graft attachment status of the study eyes will benefit the reliability, uniformity and comparability of the data of future survival studies that aim to describe `endothelial viability of DMEK grafts´ and not the ´success rate´ of the individual surgeon or within a cohort.

Reasons and outcomes of repeat DMEK

Based on these considerations, we classified reasons for 'unsuccessful DMEK' in a series of 550 primary DMEK eyes of which 17 received repeat DMEK (**Chapter 5**).[29] Corneal edema for persisting graft detachment was the main indication followed by endothelial graft failure. With minor modifications, repeat DMEK was technically feasible in all eyes and clinical outcomes were overall acceptable. However, less eyes attained the high visual acuity level as in virgin DMEK eyes. The impaired vision could be explained by the formation of corneal surface irregularities and scarring due to long-standing corneal edema, since the postoperative optical quality could be enhanced by contact lens fitting in one third of eyes.[30] To avoid secondary corneal fibrosis, it may therefore be important to not postpone the treatment of persisting DMEK detachments and graft failure for too long.

Complications after repeat DMEK were rare and resembled those of primary DMEK. Still, patients should be counseled about the possibility that certain complications may be expected to recur, as we noticed that detachments of the initial DMEK graft reappeared in the same area of the second DMEK and eyes with graft failure in the first DMEK also developed failure of the second DMEK. Causative factors may be host intrinsic characteristics, such as the eye's anatomy and comorbidities.

Prediction of DMEK rejection and transplantation of smaller endothelial grafts

A continuous ECD decrease after keratoplasty is seen as an indicator for the deterioration of a transplanted graft.[31,32] This decay may be induced and accelerated by different factors that include potential damage during the surgery itself or the presence of concomitant ocular pathologies, such as glaucoma.[33] Another important factor could derive from undetected rejection events, and from subclinical or low-grade rejection and inflammation. Allograft rejection is commonly diagnosed with slit-lamp biomicroscopy showing typical findings, such as conjunctival and/or ciliary injection, anterior uveitis, keratic precipitates, an endothelial rejection line, and corneal edema, while patients describe subjective complaints, such as photophobia, pain, and deterioration of vision that often arise prior to or at the time of the inflammatory event. DMEK eyes often appear

´quiet´, and a lower risk and milder forms of rejection that are often asymptomatic have been described. Still, an ongoing decline in ECD over time is noted that could be caused by invisible inflammation that may lead to an allograft rejection in certain cases.

Detection of subclinical inflammation

We evaluated the intraocular inflammation in 173 FECD eyes post-DMEK by assessing aqueous flare in the early and later postoperative phase with laser flare photometry (**Chapter 6**).[34] Early after DMEK, flare levels decreased quickly but after one month, they were still higher than those in healthy controls suggesting a fast but incomplete recovery of the blood-aqueous barrier. Despite the continuous application of topical steroids, also longer-term flare beyond 3 months postoperatively was higher in DMEK eyes and even higher in those associated with allograft rejection compared to virgin controls (9.2 ph/ms vs. 16.7 ph/ms vs. 7.3 ph/ms, respectively). Hence, although DMEK eyes most often appear ´silent` and uninflamed, a persistent subclinical immune response emitted by the delicate DMEK graft could contribute to a chronic ECD decrease and a higher risk of graft failure in post-rejection eyes. Still, topical steroids appear to be protective since rejection episodes increased in uncomplicated DMEK eyes after steroid cessation.[35] This observation would support the importance of permanent or indefinite steroid application post-DMEK. Interestingly, all DMEK eyes associated with rejection but also 1/3 of eyes not associated with rejection had flare values above 10 ph/ms. This flare level could be used as a threshold to identify eyes associated with or at risk of DMEK rejection. Consequently, patients with lower flare levels may be managed with regular follow-up intervals, whereas those with values above 10 ph/ms could be monitored more frequently to not miss out an upcoming (mild, slowly progressing) rejection episode.

Prediction of graft rejection

To predict DMEK rejection, we theorized that Scheimpflug imaging could be useful in revealing corneal changes that herald rejection by assessing the Scheimpflug pictures and the pachymetry maps. We retrospectively analyzed a cohort of 750 DMEK eyes and identified 17 eyes that had been diagnosed with allograft rejection (**Chapter 7**).[36] Scheimpflug images of the rejection eyes showed distinct retrocorneal elevations and/or a significant increase in pachymetry of ≥7% at the time of rejection. Interestingly, these retrocorneal peculiarities, though more subtle, were recognized in >50% of eyes on average already 8 months before rejection manifested clinically, while those delicate changes escaped detection

at the slit-lamp or simply did not appear alarming since the eyes were asymptomatic and appeared uninflamed.

Our findings suggest, that this diagnostic tool could therefore have potential in identifying DMEK eyes at risk of developing rejection many months in advance and in a phase when the patient may still be asymptomatic. Surprisingly, the inflammatory response, however, seems to be slowly building up to a full-blown rejection which contradicts previous assumptions that rejection is a T-cell–mediated immune response which usually progresses more quickly.[37,38] Since almost 25% of the rejection eyes developed secondary graft failure and because in the majority of eyes these alterations were noted about 12 months after surgery, DMEK patients may be monitored more carefully and within the first two postoperative years.

In an initial pilot study on 7 eyes with proven rejection, we observed that also endothelial cell changes, such as nuclear activation on specular microscopy preceded rejection by 1-18 months.[39] To increase the power of our prediction and potentially reduce the incidence of long-term DMEK rejections, we therefore expanded our analysis to 22 rejection eyes from a cohort of 1077 consecutive DMEK surgeries and combined the evaluation of Scheimpflug imaging (retrocorneal elevations, >7% pachymetry increase) and specular microscopy (nuclear activation and endothelial cell changes, >10% ECD decrease) to improve our algorithm for detecting eyes at risk of rejection (**Chapter 8**).[40] In this follow-up study, our retrospective analysis unveiled that over 90% of rejection eyes showed pre-rejection changes with at least one of the two diagnostics up to 6 years before rejection. Most eyes, that is about 60%, showed changes with both methods, while 25% only had changes on Scheimpflug imaging, and about 10% only on specular microscopy. The presence of subclinical keratic precipitates (retrocorneal elevations) was the most frequent early sign before rejection, followed by endothelial cell morphology changes, >10% drop in ECD and >7% pachymetry increase (82% versus 64% versus 50% versus 20%, respectively). The latter two parameters always concurred with either keratic precipitates and/or endothelial cell changes as logically the activation of the immune system may first provoke leucocyte (keratic precipitates) and endothelial cell activation (nuclear swelling), whereas endothelial cell damage or death (decrease in ECD) and corneal decompensation (increase in pachymetry) would follow thereafter.[41] Interestingly, one third of control eyes also showed changes, that, however, were less prominent, not progressing over time and limited to specular microscopy. This could be because endothelial cell changes were also described in eyes with graft failure without

rejection, whereas keratic precipitates on Scheimpflug imaging were always associated with rejection.

For clinical practice during consecutive follow-up visits of post-DMEK eyes, it could therefore be proposed to screen the posterior corneal surface with 360-degree Scheimpflug imaging to detect and document fine minute inflammatory retrocorneal deposits, to observe endothelial cell morphology, and to monitor deviations in pachymetry and ECD to predict an upcoming rejection, that could be reflected by 1. progression of deposits, 2. deterioration of cell morphology, 3. decrease in ECD and 4. increase in pachymetry over time. In case of proven progression, steroid treatment could be intensified to prevent irreversible endothelial cell damage.

Our prediction studies further illustrate that specular microscopy and Scheimpflug imaging are not only essential diagnostics to monitor the transplanted endothelial cell sheet for decay (cell decrease) and function (corneal transparency and thickness), but that both methods may be actively used to identify eyes at risk of rejection; if rejection is prevented this could benefit the preservation of the endothelial health in post-keratoplasty corneas.

For the described algorithm, however, a basic premise is that rejection occurred only beyond the third postoperative months, so that at least two images with a longer time interval in between are available before the inflammatory event, meaning that eyes with early DMEK rejection will escape detection of pre-rejection signs with this strategy because of missing baseline images.

Quarter-DMEK: utilizing multiple grafts from the same donor cornea

Quarter-DMEK was developed to improve endothelial tissue availability and to further the more efficient tissue use.[19] Theoretically, four smaller Quarter-DMEK grafts can be recovered from one donor cornea and transplanted into four recipients with central FECD. The potentially reduced antigen load placed in an eye, could additionally reduce the inflammatory reaction and graft rejection rate. The first Quarter-DMEK surgery proved feasible resulting in similar visual outcomes as in standard DMEK.[19] We then speculated whether multiple Quarter-DMEK surgeries from the same donor, thus theoretically eight grafts from one donor (four from each donor eye), would be feasible in a clinical and eye bank setting (**Chapter 9**).[42] To begin with, we transplanted two quarters from each globe of a single donor (four quarters from the bilateral pair) into four different patients on the same surgery day. We noticed acceptable visual outcomes in all four eyes,

but similar ECD decrease and complications per transplanted pair that differed from the eyes receiving the pair of the other globe. This suggests that tissue viability may vary between the globes of the same donor though processed within a short time window and in the same fashion. This could pose advantages but also new challenges, that would ask for stricter tissue quality requirements and adjustments of logistics and tissue allocation when processing several grafts from one donor. On the other hand, this concept could offer a vivid in vivo tissue ´quality check´ that to some extend would permit anticipation on the surgery outcomes and complications. Consequently, only if transplantation of the first quadrant of the Descemet sheet from one globe shows favorable graft viability with an uncomplicated course in the first week, then the remaining three quadrants should be released for surgery.

FINAL REMARKS AND FUTURE PERSPECTIVES

After almost 15 years since the first surgery, DMEK has evolved to a standard procedure that also provides excellent long-term clinical outcomes and graft longevity.[20] In the event of corneal edema from graft failure or persistent graft dehiscence, repeat DMEK is a feasible and successful procedure which, when promptly employed, can avoid inferior visual outcomes from anterior corneal surface scarring that may require contact lens correction.

A long-term goal in the management of post-DMEK eyes is to increase graft longevity.[20] This could be targeted by reducing the continuous ECD decrease that may originate from an ongoing inflammation caused by the foreign DMEK tissue. Visualization of the invisible immune reaction to adjust post-DMEK treatment could therefore reduce endothelial cell decay.

In addition, active prediction, and detection instead of passive observation and anticipation of rejection could prevent and reduce long-term rejection by timely treatment to minimize the ´silent` cell damage and subsequent graft failure. Besides the already existing diagnostic devices in ophthalmology, the application of further tools or the development of new technologies could help in making an upcoming rejection diagnostically visible. Ideally, this could be supported by automated recognition and artificial intelligence so that detection would be independent of the examiners experience and would allow a more secure, quick, and standardized follow-up of the rapidly increasing numbers of post-DMEK eyes worldwide.

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