Off-Centered DMEK Grafts: Impact and Resolution

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Purpose: The aim of this study was to assess the outcomes of off-centered Descemet membrane endothelial keratoplasty (DMEK) grafts compared to descemetorhexis.

Methods: This is a retrospective case series of DMEK procedures conducted between June 2022 and July 2023 with postoperative graft decentration, characterized by a gap between the graft and descemetorhexis edge.

Results: Eight eyes of 8 patients met the inclusion criteria. The average gap between the descemetorhexis edge and DMEK graft was 911.2 μm (range 306–1468). The resulting focal peripheral edema overlying the gap resolved in all cases, with a median time of 3 months. Best-corrected visual acuity improved from 0.49 (±0.26) logarithm of the minimum angle of resolution to 0.01 (±0.02) logarithm of the minimum angle of resolution at 12 months (P = 0.003). Central corneal thickness decreased from 646.5 (±177.8) μm to 473.7 (±29.6) μm at 12 months (P = 0.05). One eye, in the overlapped area of host–donor Descemet membranes, had small peripheral partial graft detachment less than one-third of graft surface area. No eyes required graft rebubbling. A larger descemetorhexis to DMEK gap showed a trend toward longer resolution times (P = 0.06). Focal edema in the inferonasal periphery took longer to recover compared with the nasal position (P = 0.01). Larger descemetorhexis to DMEK gaps did not significantly influence the longitudinal visual acuity trend (P = 0.75).

Conclusions: Decentered DMEK, characterized by a gap between the graft and descemetorhexis edge, leads to focal stromal edema that diminishes over time, with no impact on final visual acuity.

Key Words: DMEK, centration, rhexis, alignment, rebubbling, cornea

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INTRODUCTION

Descemet membrane endothelial keratoplasty (DMEK) is specifically designed to address conditions affecting the corneal endothelium,[1,2] such as Fuchs endothelial dystrophy (FED) and bullous keratopathy (BK), which lead to endothelial dysfunction with subsequent corneal edema and vision impairment, thus making them prime candidates for DMEK.[3] Particularly, in cases of FED, descemetorhexis plays a crucial role, involving the precise removal of Descemet membrane (DM) and the endothelial layer. The accuracy of this step is paramount as it significantly influences the outcomes and success of the graft. The optimal size of descemetorhexis remains a topic of debate, varying according to surgeon preference, underlying disease (FED or BK), and the donor graft size.[3] A well-sized descemetorhexis without tags is critical for ensuring the donor graft attaches firmly to the recipient's corneal stroma. If the rhexis is too small, it may result in poor graft adherence or increased risk of graft dislocation, while an excessively large rhexis may fail to cover the entire area, potentially leading to peripheral corneal edema.[3] However, the literature still lacks comprehensive insights into the outcomes of decentered DMEK grafts. In light of these considerations, we present a case series focusing on off-centered DMEK grafts, their consequences, resolution, and the surgical techniques used to center the graft.

MATERIALS AND METHODS

This study comprised a case series of patients undergoing DMEK surgery at the "ASST Spedali Civili di Brescia Hospital" (Brescia, Italy) between July 2022 and June 2023, who exhibited postoperative descemetorhexis–DMEK graft gap. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

Participants

All patients who underwent uncomplicated DMEK surgery, with preoperative and postoperative anterior segment optical coherence tomography (AS-OCT), central corneal thickness (CCT) measurements, and recorded best-corrected visual acuity (BCVA), were included for analysis. Exclusion criteria encompassed the absence of preoperative/

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postoperative AS-OCT scans and intraoperative or early postoperative complications, such as prolonged pupillary block, air/gas bubble dislocation, upside-down graft, complete graft detachment with a free-floating graft in the anterior chamber (AC), or folded graft. AS-OCT images and CCT measurements were obtained using the CASIA2 (Tomey Corporation, Nagoya, Aichi Prefecture, Japan).

Descemetorhexis–DMEK graft gap was defined as the longest linear distance between the DMEK graft edge and inner edge of the host descemetorhexis, as identified by AS-OCT and measured in μm with the built-in caliper function (Fig. 1).

Focal corneal stromal edema was quantified using the pachymetry map provided by CASIA2 system. In addition, the time taken for the resolution of focal peripheral edema, corresponding to a normalization of the corneal thickness profile on pachymetry map, was documented.

Variables and Outcomes

The primary outcome was to determine the influence of descemetorhexis–DMEK graft gap on the longitudinal trend of BCVA after DMEK surgery. Secondary outcomes included the influence of descemetorhexis–DMEK graft gap on the resolution time of the focal peripheral corneal edema.

Statistical Analysis

Descriptive data were summarized using the mean (SD), median (interquartile range), and number (percentages) where appropriate. Paired *t*-tests were used to compare the change in preoperative and final values of BCVA, CCT, and spherical equivalent refraction.

A generalized linear model with a Poisson distribution was used to investigate the correlation between the time taken for focal peripheral corneal edema resolution and independent variables, including the extent of the descemethorexis–DMEK gap, age at surgery, location of the peripheral edema, and gender.

Furthermore, a linear mixed-effects model was used to investigate the effect of the descemethorexis–DMEK gap measurement on BCVA. This model incorporated an interaction term with months after surgery and included an eye-level term with random intercept and random slope over time to account for intrapatient correlation.

A *P* value less than 0.05 was considered statistically significant. All analyses were performed using R software version 4.2.2 (R Project for Statistical Computing, Vienna, Austria).

RESULTS

A total of 8 eyes of 8 patients met the inclusion criteria, with a mean (SD) age at surgery of 70.6 (±8.9) years and 5 (62.5%) patients being female. All patients have FED, with no cases of BK met the criteria. Moreover, all patients were pseudophakic at the time of surgery. In all patients, DMEK procedure was performed as following. In brief, a 7.5-mm donor graft was prepared with "yogurt" technique, using the Tzamalis punch; an 8.00-mm descemetorhexis was performed under air in all cases, with surgical peripheral iridotomy facilitated by a 20G anterior vitrectome intraoperatively.[4] The absence of DM tags was confirmed by filling the AC with air after descemetorhexis, and 20% sulfur hexafluoride was used as tamponade.

Improvement in BCVA was observed in all cases, with a baseline mean (SD) of 0.49 (±0.26) logarithm of the minimum angle of resolution (logMAR) improving to 0.01 (±0.02) logMAR at 12 months (*P* = 0.003). Similarly, the average CCT decreased from 646.5 (±177.8) μm to 473.7 (±29.6) μm at 12 months (*P* = 0.05). In addition, the average spherical equivalent slightly increased from 0 (±0.99) to 0.125 (±0.82) D at 12 months (*P* = 0.02).

One eye had small peripheral partial graft detachment less than one-third of graft surface area, at area of overlap host–donor Descemet membranes (Fig. 2).[5] No eyes required graft rebubbling, as summarized in Table 1. Endothelial cell density declined from 2786 ± 291 cells/mm^2, at baseline, to 1120 ± 371 cells/mm^2 at 12 months.

At postoperative AS-OCT images, the average distance between the descemetorhexis edge and DMEK graft was 911.2 μm (range 306–1468). Focal peripheral edema

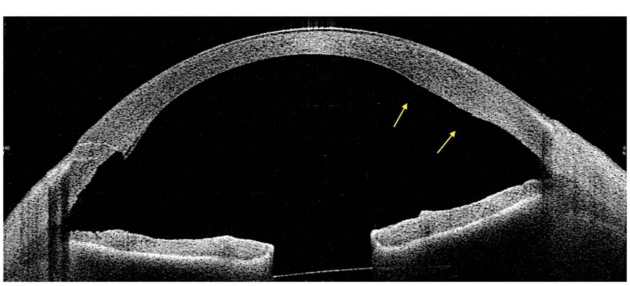

FIGURE 1. Example of descemetorhexis–DMEK gap and overlying focal edema (pointed by yellow arrows). (The full color version of this figure is available at www.corneajrnl.com.)

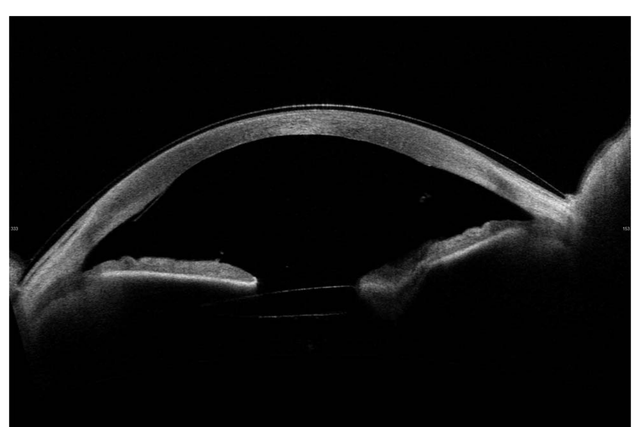

FIGURE 2. Peripheral partial graft detachment less than one-third of graft surface area, not requiring rebubbling, in the area of overlapping area of donor–host DM.

TABLE 1. Baseline and Final Characteristics of Included Patients

Eyes, n	8
Females, n (%)	5 (62.5%)
Indication	
FED, n (%)	8 (100%)
Age at surgery, years—mean (SD)	70.6 (8.9)
Baseline	
Visual acuity, logMAR—mean (SD)	0.49 (±0.26)
Central corneal thickness, μm—mean (SD)	646.5 (±177.8)
Spherical equivalent, D—mean (SD)	0 (±0.99)
Donor ECD, cells/mm^2—mean (SD)	2785.7 (±291.1)
Postoperative follow-up	
Rebubbling, n (%)	0 (0%)
Descemetorhexis–DMEK gap, μm—mean (SD)	911.2 (±474.3)
Time to edema resolution, months—median (IQR)	3 (2, 6.25)
12 mo	
Visual acuity, logMAR—mean (SD)	0.01 (±0.02)
Central corneal thickness, μm—mean (SD)	473.7 (±29.6)
Spherical equivalent, D—mean (SD)	0.125 (±0.82)
Final ECD, cells/mm^2—mean (SD)	1120 (±371.4)

ECD, endothelial cell density.

correspondence to areas of bare stroma resolved in all cases, as evidenced by the normalization of the isopachs at pachymetry maps (Figs. 3 and 4).[6] The median (interquartile range) time to resolution of peripheral edema was 3 (2, 6.25) months.

In investigating the effect of independent variables on time to edema resolution using a Poisson model, larger descemetorhexis–DMEK gap measures exhibited a trend toward longer resolution times (Fig. 5A), though this associated did not reach significance (P = 0.06). Similarly, older age at surgery showed a nonsignificant trend toward longer resolution times (Fig. 5B, P = 0.12). Focal edema in the inferonasal periphery took longer to resolve compared with the nasal position (Fig. 5C, P = 0.01), with no significant differences observed in the superotemporal quadrant. Furthermore, male gender was associated with longer recovery periods (Fig. 5D, P = 0.002).

In a linear mixed-effects model exploring the impact of descemetorhexis–DMEK gaps on visual acuity during the first year after surgery, larger gaps did not significantly affect the longitudinal visual acuity trend (Fig. 6, P = 0.75).

DISCUSSION

Attention to detail is crucial in DMEK surgery, as it profoundly influences surgical outcomes and postoperative recovery.[7] While numerous studies have investigated various aspects of DMEK surgery, such as graft attachment and visual outcomes, there remains a conspicuous gap in the literature concerning peripheral edema and residual irregularities of the posterior corneal surface after DMEK surgery.[8–10] Despite often being overlooked, these 2 factors may exert a significant impact on the long-term success of the graft and patient's comfort.

Ensuring a smooth landing zone, characterized by a descemetorhexis without the presence of tags, is vital to minimizing the risk of graft detachment and postoperative corneal opacities.[11–14]

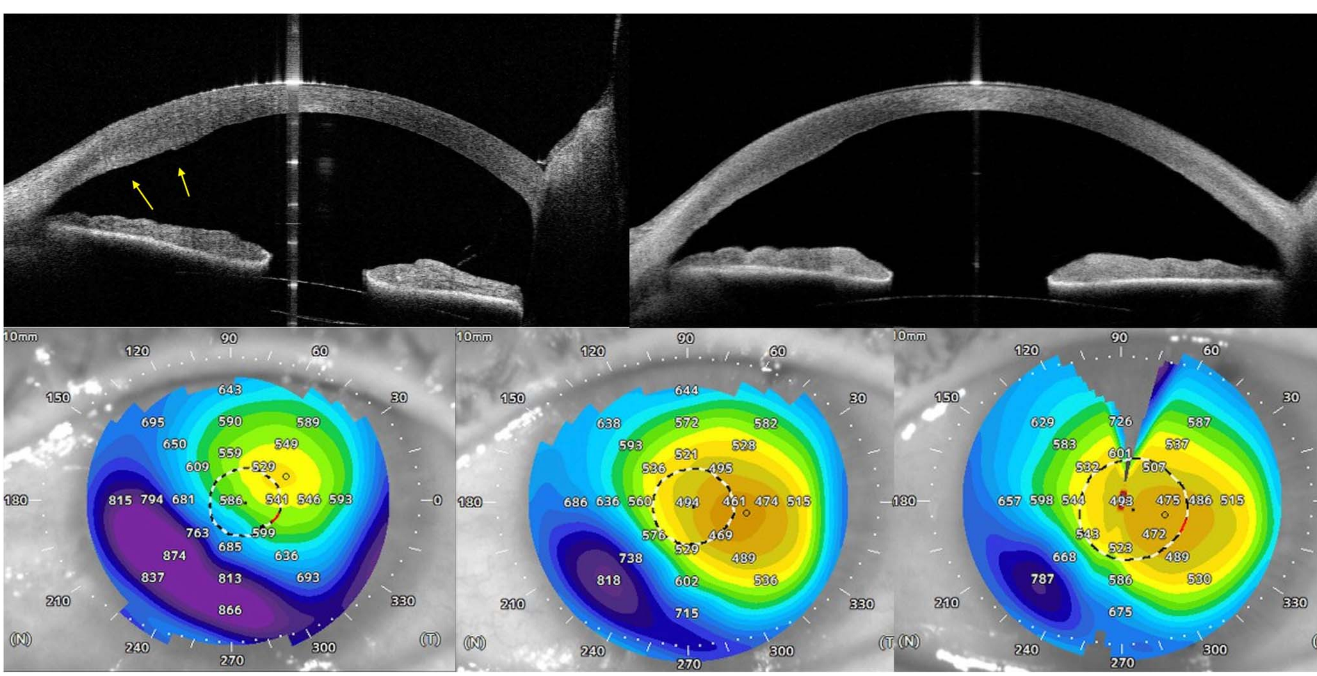

FIGURE 3. Example of descemetorhexis–DMEK gap, the overlying focal edema (pointed by yellow arrows), and pachymetry map changes over time. (The full color version of this figure is available at www.corneajrnl.com.)

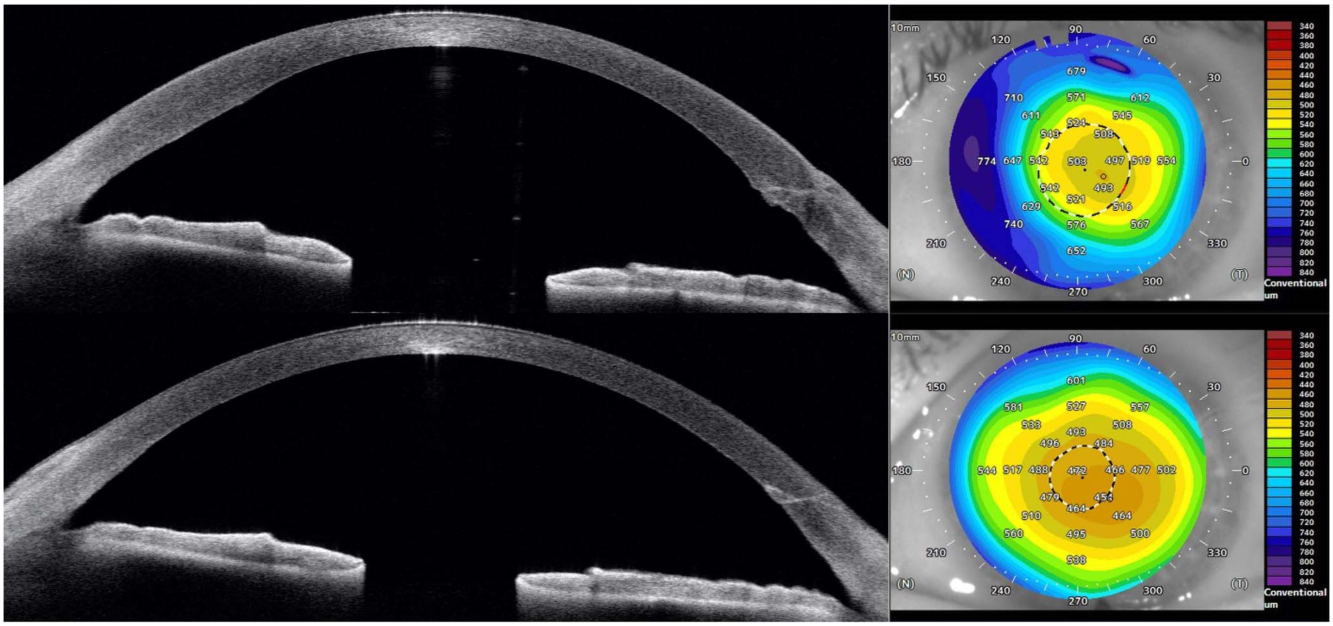

FIGURE 4. Example of resolution of nasal focal edema due to descemetorhexis–DMEK gap (1 month versus 3 months). (The full color version of this figure is available at www.corneajrnl.com.)

Descemetorhexis can be performed using balanced salt solution (BSS), ophthalmic viscosurgical devices (OVDs), or by introducing air into the AC.[15,16] However, when conducted using BSS or OVDs, the visibility of DM is suboptimal compared with the visibility achieved when air is injected into the AC.[17–20] Many approaches have also been proposed to enhance the visualization of peripheral DM tags.[21]

The descemetorhexis to graft size ratio emerges as a critical consideration before undertaking endothelial keratoplasty, especially in cases involving preloaded grafts where assessment is not feasible during surgery. Typically, descemetorhexis is intended to be slightly larger than the graft size to prevent overlap with DM remnants.[22] Parekh et al[3] evaluated the benefits and drawbacks of various graft sizes, recommending that novice surgeons commence with standard 7.5-mm grafts, gradually transitioning to larger or smaller grafts based on the patient requirements. However, smaller grafts present limitations such as challenges in peeling and maintaining endothelial cell viability, potentially resulting in higher endothelial cell loss. On the other side, larger grafts offer advantages such as increased endothelial cell count for

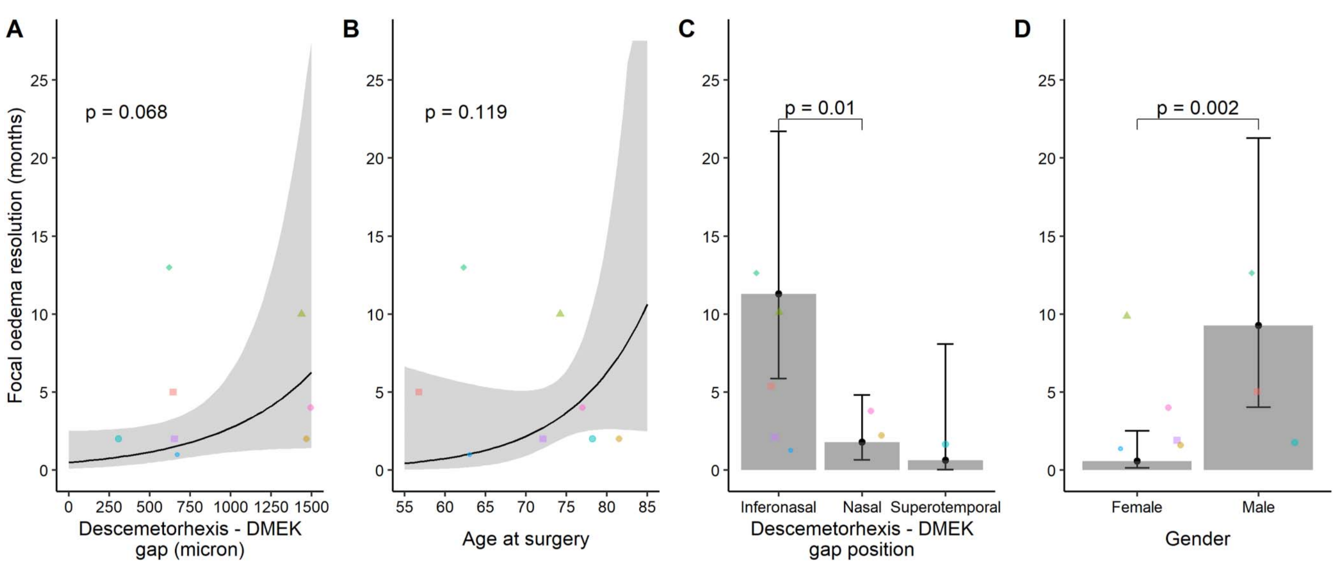

FIGURE 5. Effect of independent variables on time to edema resolution. A, descemetorhexis–DMEK gap size; B, age at surgery; C, localization of edema; and D, host sex. (The full color version of this figure is available at www.corneajrnl.com.)

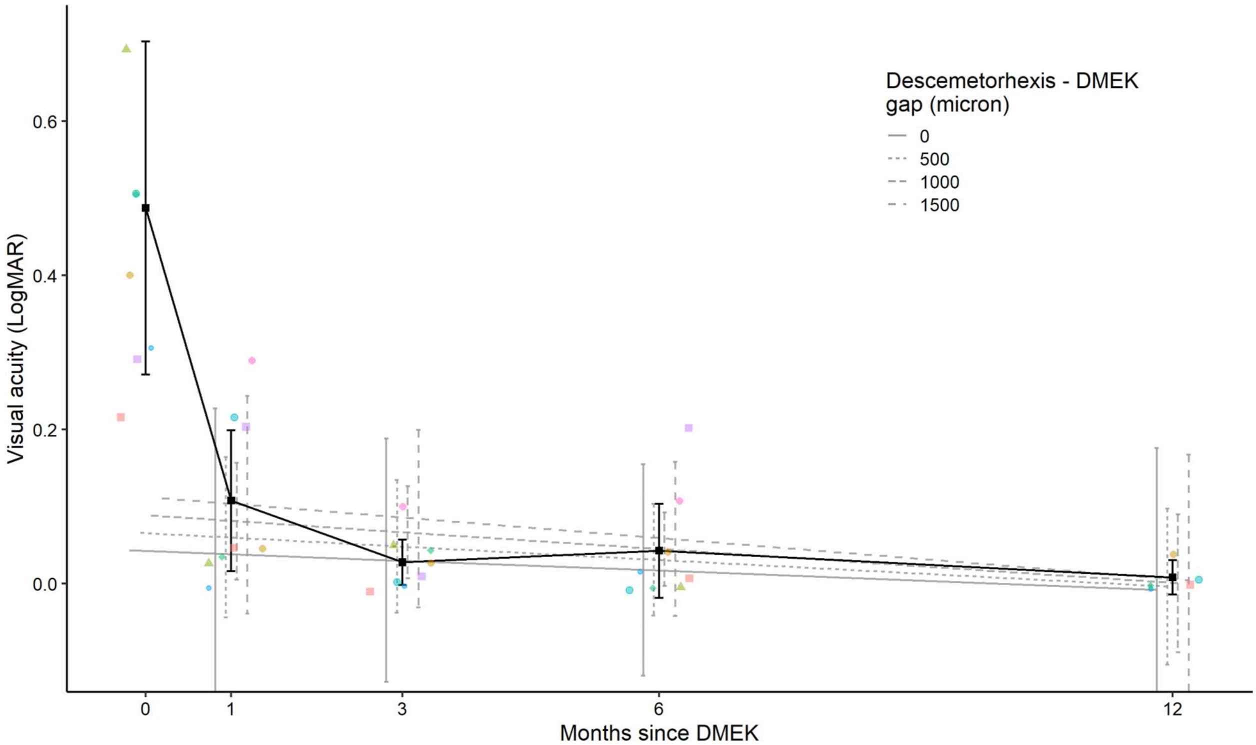

FIGURE 6. Effect of descemetorhexis–DMEK gap size and postoperative visual acuity. (The full color version of this figure is available at www.corneajrnl.com.)

transplantation, ease of preparation and loading, and improved handling during transplantation, enhancing long-term graft survival. However, larger-diameter grafts may pose challenges during attachment and cause elevated detachment rates. Therefore, customization of descemetorhexis and graft sizes based on the specific clinical context is emphasized, emphasizing the importance of individualized approaches over a one-size-fits-all strategy.

Another critical aspect of this surgical procedure is the precise centering of the graft, aiming to minimizing the risk of graft decentration, which can lead to a double effect of a gap on one side and overlapping on the other side between the edges of the graft. Two techniques can be used to center the graft, depending on its folding status. If the DMEK graft is already unfolded but decentered, the "wave maneuver," as described by Lavy et al,[23] is recommended.

The technique involves injecting a small air bubble beneath the graft and deepening the AC with BSS. Subsequently, swift taps are applied on the cornea toward the center, facilitating the "sliding" of the graft on the BSS–air interface. Based on our experience, the air bubble should not exceed approximately 3 mm in size, as larger air bubble may diminish the fluid meniscus, potentially trapping the graft and impeding its sliding ability (Video 1).

Alternatively, when dealing with a folded graft (Video 2) rather than a decentered one, another technique we have used involved entering the AC with a blunt cannula, positioning it within the fold, gently maneuvering the graft toward the periphery, and then evacuating the AC by lowering the lip of the main incision. The outflow of fluid typically aids in unfolding the proximal side of the graft. To recover it, gentle tapping with 2 blunt cannulas on the edge of the main incision is performed (Video 2).

Regarding the outcomes of decentered DMEK grafts with gaps between the graft and descemetorhexis edges, several considerations arise. The observed early decreased in endothelial cell count at 6 months (approximately 25%) has traditionally been attributed to intraoperative manipulations during the unfolding and centering procedures.[24] However, recent insights suggest that donor endothelial cells possess the ability to migrate to exposed recipient areas, and decentering does not appear to correlate with the final visual outcome, provided the central area remains covered by the graft.[25,26] This phenomenon is evident in our study as well, where postoperative focal edema did not adversely affect the final BCVA.[27]

Rock et al conducted a comparative analysis between 2 groups: well-centered grafts, which exhibited a detachment rate of 12%, versus decentered grafts, where 87% experienced detachment at the 12-month follow-up.[28] The primary risk associated with decentration, therefore, lies in the potential overlap with residual peripheral DM tags and subsequent postoperative graft detachment rather than a lack of transplantation efficacy.[13,29] Recent findings emphasize the importance of considering the direction of graft shift. Inferior graft shift has been correlated with higher postoperative graft detachment rates, whereas superior graft shift has shown a positive impact on postoperative corneal endothelial values.

Grafts shifted superiorly would have prolonged contact with the air bubble tamponade and less exposure to inflammatory cytokines in the aqueous humor. Therefore, it has been recommended avoiding inferior graft shift, as this is the quadrant where detachment most frequently occurs.[22,30]

In our study, despite graft decentration resulting in both a gap with the descemetorhexis and overlapping with the host DM, we did not observe any grafts requiring postoperative rebubbling. This could be attributed to either the small number of patients meeting the inclusion criteria and/or meticulous inspection of the host cornea after descemetorhexis, which revealed no DM tags.

The resolution of focal stromal edema overlying the area of the gap may be attributed to the restoration of pump activity facilitated by DMEK and/or effect of descemetorhexis on endothelial cell migration.

Endothelial cells are known to possess the ability to migrate over exposed recipient areas and vice versa.[26,31,32] Another concept underlying cell migration and proliferation is contact inhibition. It has been indicated that the decrease in corneal edema typically happens at the opposite end of the DMEK attachment site, suggesting that the recovery predominantly originates from recipient cells rather than donor cells.[26] Creating a descemetorhexis may disrupt contact inhibition, a mechanism that maintains endothelial cells in a dormant state, potentially triggering their activation and proliferation.[33,34]

A recent study investigated the role of DM in corneal endothelial wound healing using in vivo rabbit models. Following corneal endothelial cell scraping, transient fibrotic endothelial–mesenchymal transition occurred, reverting to an endothelial phenotype by day 14. Conversely, DM stripping led to fibroblastic cells in posterior fibrosis tissue, suggesting that DM supports corneal endothelial cell regeneration. Of note, using a stripping injury method revealed the formation of retrocorneal fibrous membrane. After Descemet membrane removal, the underlying stroma was exposed to the aqueous humor, which contains growth factors such as members of the transforming growth factor-beta family. This exposure may have activated keratocytes near the wound site, prompting their differentiation into alpha smooth muscle actin (α-SMA–positive) myofibroblasts.[35] The impact of transforming growth factor-beta on keratocytes has been extensively studied in prior studies.[36,37] The formation of this retrocorneal fibrous membrane could potentially facilitate endothelial cell migration.

In our case, only patients with FED met the inclusion criteria. Further studies, including patients with BK, are advisable for 2 reasons. First, in case of FED, peripheral host endothelial cell density is adequate to possibly migrate and to resolve the focal edema over time, whereas in case of BK may not be.[38] Second, peripheral corneal thickness in case of DMEK for BK is thicker compared with DMEK for FED, with possible different behaviors in resolution of focal edema overlying possible gaps.[39,40]

Peripheral edema typically resolves over time through cell migration and regeneration of the endothelial pump. However, there are instances where resolution does not occur, potentially leading to postoperative complications. Parekh et al documented a case involving an intraoperative complication during large (9.5 mm) ultra-thin Descemet stripping automated endothelial keratoplasty surgery, necessitating a conversion to DMEK surgery (7.75 mm). At the 5-month follow-up, the patient achieved a best spectacle-corrected visual acuity of 6/6 (20/20) in the left eye but experienced mild discomfort. A circular ring of corneal edema was observed around the graft, along with decentralization of the transplanted graft. Despite the potential for endothelial cell migration to cover the gap, this process appeared inconsistent in this case, as evidenced by insufficient bridging of the circumferential gap of 1.75 mm.[41]

Another aspect to consider is the presence of proinflammatory cytokines in the aqueous humor preoperatively and postoperatively. Preoperative levels of aqueous cytokines are associated with a reduction in endothelial cells after corneal transplantation.[42–44]

An augmented innate immune response was identified in failed DMEK grafts, indicating the involvement of non–T-cell mediators in the pathogenesis of DMEK failure.[45] Conversely, the levels of various proinflammatory cytokines in the aqueous humor notably decreased following DMEK, suggesting a potential reduction in AC inflammation due to the restoration of endothelial pump function following transplantation of healthy endothelium.[46]

Prolonged corneal edema resulting from increased exposure of bare stroma may be associated with elevated levels of inflammatory cytokines. Further research is warranted to investigate the correlation between the inflammatory state of the aqueous humor and extent of stromal exposure subsequent to endothelial transplantation procedures.

Regarding the endothelial cell loss at 12 months in off-centered DMEK grafts, in our case, we observed higher decrease compared with general literature regarding DMEK and endothelial cell loss (59.8% vs. 35.5%).[27,47] However, this could be due to small sample size and/or lack of subgroup evaluation of decentered DMEK in the literature up to date. In addition, it is also possible that endothelial cells migrate from the center to the area of gap, with subsequent reduction in central endothelial density.

In conclusion, off-centered DMEK procedures yield satisfactory final BCVA, and any focal stromal edema observed in the area of the gap appears to be transient. However, further research with larger sample size, longer follow-up time, and evaluation in patients with BK is warranted to provide deeper insights into this phenomenon.

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