TEN-YEAR EXPERIENCE IN DESCEMET'S MEMBRANE ENDOTHELIAL KERATOPLASTY IN A SINGLE-CENTER — WHAT HAVE WE LEARNT

ANNEX - PUBLICATIONS

NUNO MIGUEL DE MOURA ANTUNES E VALEJO COELHO

A thesis submitted in fulfilment of the requirements for the Doctoral Degree in Medicine at Faculdade de Ciências Médicas | NOVA Medical School of NOVA University Lisbon

March 2024

TEN-YEAR EXPERIENCE IN DESCEMET'S MEMBRANE ENDOTHELIAL KERATOPLASTY IN A SINGLE-CENTER — WHAT HAVE WE LEARNT

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The author is the sole responsible for the opinions expressed in this publication.

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LIST OF SCIENTIFIC PUBLICATIONS

The present Doctoral Thesis is based on the following published scientific papers by the Candidate, which are presented in their entireness in the Annex.

I – Moura-Coelho, N., Manero, F., Elies, D., Amich, N., Morral, M., Gris, O., & Güell, J. (2020). Repeat Descemet Membrane Endothelial Keratoplasty for Failed Primary Descemet Membrane Endothelial Keratoplasty at a Referral Center for Keratoplasty in Spain: DIMOEK Study. *American journal of ophthalmology*, *215*, 49–55. https://doi.org/10.1016/j.ajo.2020.03.015.

II – Moura-Coelho, N., Cunha, J.P., Morral, M., Gris, O., Manero, F., & Güell, J.L. (2021a). Secondary Endothelial Keratoplasty-A Narrative Review of the Outcomes of Secondary Corneal Endothelial Allografts. *Transplantation*, *105*(12), e347–e365. https://doi.org/10.1097/TP.0000000000003735.

III – Moura-Coelho, N., Cunha, J.P., Amich, N., Gris, O., Manero, F., & Güell, J.L. (2021b). "*Secondary DMEK after Failed DSEK Graft in Complex Eyes – Retrospective Case Series*." *Journal of EuCornea*, September 2021.

IV – Moura-Coelho, N., Cunha, J.P., Dias-Santos, A., Dutra-Medeiros, M., Papa-Vettorazzi, R., Manero, F., & Güell, J. (2023a). Descemet's Membrane Endothelial Keratoplasty for Corneal Endothelial Failure Secondary to Three Types of Phakic Intraocular Lens - Retrospective Study. *Clinical ophthalmology (Auckland, N.Z.)*, *17*, 931–940. https://doi.org/10.2147/OPTH.S401387.

V – Moura-Coelho, N., Papa-Vettorazzi, R., Santiesteban-García, I., Dias-Santos, A., Manero, F., Cunha, J.P., & Güell, J. (2023b). Outcomes of cystoid macular edema following Descemet's membrane endothelial keratoplasty in a referral center for keratoplasty in Spain: retrospective study. *Scientific reports*, *13*(1), 2375. https://doi.org/10.1038/s41598-023-29127-5.

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VII – Moura-Coelho, N., Cunha, J.P., Papa-Vettorazzi, R., Gris, Ó., & Güell, J.L. (2023d). Acute corneal allograft rejection following SARS-CoV-2 vaccination-A systematic review. *Acta ophthalmologica*, *101*(1), e1–e13. https://doi.org/10.1111/aos.15211.

VIII – Moura-Coelho, N., Papa-Vettorazzi, R., Reyes, A., Cunha, J.P., & Güell, J.L. (2023e). Ultrathin DSAEK versus DMEK - Review of systematic

reviews. *European journal of ophthalmology*, 11206721231214605. Advance online publication. https://doi.org/10.1177/11206721231214605.

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X – Moura-Coelho, N., Arrondo, E., Papa-Vettorazzi, M. R., Cunha, J.P., & Güell, J.L. (2022a). DMEK for the treatment of interface fluid syndrome secondary to failed DSAEK graft: A case report and review of the literature. *American journal of ophthalmology case reports*, *27*, 101656. https://doi.org/10.1016/j.ajoc.2022.101656.

XI – Moura-Coelho, N., Papa-Vettorazzi, M.R., Dias-Santos, A., Cunha, J.P., Dutra-Medeiros, M., Manero, F., & Güell, J.L. (2024) *Predictive factors for graft failure after primary DMEK surgery - retrospective cohort study.* [Submitted].

XII – Moura-Coelho, N., Papa-Vettorazzi, M.R., Dias-Santos, A., Cunha, J.P., Dutra-Medeiros, M., Manero, F., & Güell, J.L. (2024) *Predictive factors of long-term visual outcomes after primary Descemet's membrane endothelial keratoplasty (DMEK) - retrospective study.* [Submitted].

XIII – Moura-Coelho, N., Papa-Vettorazzi, M.R., Reyes, A., Cunha, J.P., Dutra-Medeiros, M., Manero, F., & Güell, J.L. (2024) *Intraocular lens opacification following Descemet's membrane endothelial keratoplasty – risk factors and outcomes after intraocular lens exchange*. [Submitted].

XIV – Alonso-Reyes, H., Moura-Coelho, N., Lindez-Pérez, E., & Güell, J.L. (2024) *DMEK surgical strategy in aphakic and vitreous disease.* [Submitted].

XV – Moura-Coelho, N., Gris, O., & Güell, J.L. (2023f) Descripción de la técnica quirúrgica básica de DMEK. *In: Queratoplastias Laminares – Actualización en técnicas quirúrgicas y aspectos refractivos*. Sociedad Española de Cirugía Ocular Implanto-Refractiva 2023. ISBN 978-84-939898-9-7.

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XVII – Moura-Coelho, N., & Güell, J.L. (2023h, in press) Cataract surgery in combination with corneal surgery. In: Pardianto G, Tassignon MJ, editors. Textbook of Innovations in Cataract Surgery. Singapore: Springer; c2023.

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XIX – Moura-Coelho, N., & Güell, J.L. (2021c) *Queratoplastia laminar endotelial In: Cirugia corneal y refractiva – Libro de residentes de la Sociedad Española de Oftalmología*.

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XXII – Moura-Coelho, N., & Güell, J.L. (2022b) Refractive Accuracy after Cataract Surgery and Descemet's Membrane Endothelial Keratoplasty. *Cataract and Refractive Surgery Today*, September 2022 Issue. https://crstoday.com/articles/2022-sept/refractive-accuracy-after-cataract-surgery-and-descemet-membrane-endothelial-keratoplasty.

XXIII – Moura-Coelho, N. (2023i) Safe and effective: DMEK after penetrating keratoplasty. *European Ophthalmology News at 41st Congress of the ESCRS* 2023. Page 21.

XXIV – Cunha, J.P., Moura-Coelho, N., Pinto Proença, R., Dias Santos, A., & Tavares Ferreira, J. (2020) COVID-19: An Ophthalmologist's Perspective. Gaz Med [Internet]. 2020 Jun. 29 [cited 2024 Mar. 18];7(2). Available from: https://www.gazetamedica.pt/index.php/gazeta/article/view/317.

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Publication I

Repeat Descemet Membrane Endothelial Keratoplasty for Failed Primary Descemet Membrane Endothelial Keratoplasty at a Referral Center for Keratoplasty in Spain: DIMOEK Study

NUNO MOURA-COELHO, FELICIDAD MANERO, DANIEL ELIES, NICOLÁS AMICH, MERCE MORRAL, OSCAR GRIS, AND JOSÉ GÜELL

• PURPOSE: To analyze the clinical results of repeat Descemet membrane endothelial keratoplasty (re-DMEK) for failed primary DMEK graft at a referral center for keratoplasty in Spain.

• DESIGN: Retrospective, interventional, comparative case series.

• METHODS: From a single-center, single-surgeon series of 189 consecutive DMEK surgeries, 14 (7.41%) were re-DMEK eyes. The primary outcome was best-corrected visual acuity change (ΔBCVA, logarithm of minimal angle of resolution [logMAR]) from baseline (before first DMEK) to last follow-up. Secondary outcomes were ΔBCVA from baseline at 3, 6, and 12 months postoperatively, endothelial cell loss (%ECL), rebubbling rate, and re-DMEK graft failure. Outcomes were compared with an age-matched control group of 18 successful primary DMEK eyes.

• RESULTS: After re-DMEK (median follow-up time 14.5 [42.5] months), mean BCVA improved from 0.55 (0.42) logMAR (Snellen 20/71 [20/53]) at baseline to 0.09 (0.26) logMAR (Snellen 20/25 [20/36]; $P = .037$). ΔBCVA from baseline was statistically significant at months 3 ($P = .028$), 6 ($P = .023$), and 12 ($P = .012$), and ΔBCVA was significant observed between months 6 and 12 ($P = .028$). BCVA differences between patient groups were statistically nonsignificant at 3 ($P = .397$), 6 ($P = .468$), and 12 months ($P = .647$). Mean % ECL in re-DMEK eyes with follow-up ≥12 months was 48.2 (15.1%), and the rebubbling rate was 28.6%; differences between groups were statistically nonsignificant for both variables ($P = .580$ and $P = .669$, respectively). Three re-DMEK eyes developed graft failure, all achieving final BCVA ≤0.30 logMAR (Snellen ≥20/40) after tertiary keratoplasty.

• CONCLUSIONS: Repeat DMEK produces significant, continuous visual improvement after failed primary DMEK. Although visual outcomes and %ECL were comparable to primary DMEK, there was a relatively high rate of graft failure after re-DMEK. (Am J Ophthalmol 2020;215:49–55. © 2020 Elsevier Inc. All rights reserved.)

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ENDOTHELIAL KERATOPLASTY (EK) IS CURRENTLY considered the gold standard for the management of corneal endothelial disease, particularly Descemet membrane endothelial keratoplasty (DMEK)[1,2] given the benefits over penetrating keratoplasty (PKP) and Descemet stripping endothelial keratoplasty (DSEK).[3] However, DMEK grafts are also at risk of developing graft failure. Although clinical outcomes of repeat keratoplasty have been well documented in eyes with previously failed PKP (including repeat PKP[4,5] and DSEK/DMEK under failed PKP[6–11]) and in eyes with previously failed DSEK grafts (repeat DSEK[12,13] or DMEK[14–18]), clinical evidence of the functional results of repeat DMEK for failed primary DMEK grafts (re-DMEK) is limited at present.[2,19–22]

Our aim was to analyze the clinical outcomes of repeat DMEK surgeries performed at our institution and to compare outcomes between re-DMEK and successful primary DMEK.

METHODS

• STUDY DESIGN AND APPROVAL: This was a retrospective, interventional, comparative case series. Eyes that underwent re-DMEK for failed primary DMEK were compared with an age-matched control group of successful primary DMEK eyes. All patients signed an institutional review board–approved informed consent. The study was conducted according to the tenets of the Declaration of Helsinki.

• PATIENTS: From a single-center, single-surgeon (J.G.) series of 189 consecutive DMEK surgeries performed

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TABLE 1. Demographics of the Repeat Descemet Membrane Endothelial Keratoplasty Group and an Age-Matched Control Group of Successful Primary Descemet Membrane Endothelial Keratoplasty Eyes

Variable	Repeat DMEK (n = 14)	Control Group (n = 18)	*P* Value
Patient age, years (SD)	68.4 (9.0)	66.2 (10.0)	.781
Female gender, n (%)	11 (78.6)	14 (77.8)	.617
Laterality, right eyes, n (%)	5 (35.7)	8 (44.4)	.447
Etiology of corneal disease,[a] n (%)			
FECD	11 (78.6)	14 (77.8)	—
PPBK	2 (14.3)	3 (16.7)	—
Other	1 (7.1)	1 (5.6)	—
Lens status at the time of primary DMEK surgery,[b] n (%)			
Phakic	3 (21.4)	0	—
Pseudophakic	11 (78.6)	18 (100.0)	—
BCVA before primary DMEK, logMAR (SD)	0.55 (0.42)	0.59 (0.47)	.587
Patients with ocular comorbidities,[c] n (%)	5 (35.7)	6 (33.3)	.590
Etiology of primary DMEK failure, n (%)			
PGF	8 (57.1)	—	—
SGF	4 (28.6)	—	—
Immune rejection	2 (14.3)	—	—
Need of rebubbling in failed primary DMEK grafts, n (%)	4 (28.6)	—	—
BCVA before re-DMEK (logMAR)	1.30 (0.65)	—	—

BCVA = best-corrected visual acuity; DMEK = Descemet membrane endothelial keratoplasty; FECD = Fuchs endothelial corneal dystrophy; PGF = primary graft failure; PPBK = pseudophakic bullous keratopathy; SD = standard deviation; SGF = secondary graft failure.

[a]In the repeat DMEK group, 1 eye (7.1%) had undergone primary DMEK surgery for previously failed penetrating keratoplasty. In the control group, 1 eye (5.6%) had undergone primary DMEK surgery after phakic intraocular lens explantation and cataract surgery with corneal decompensation.

[b]All eyes were pseudophakic at the time of repeat DMEK surgery. At the time of primary DMEK in the repeat DMEK group, phakic eyes (3 eyes, 21.4%) underwent triple procedure (DMEK combined with cataract surgery by phacoemulsification with intraocular lens implantation); 7 eyes (50%) had sequential cataract surgery followed by primary DMEK.

[c]In the repeat DMEK group, 2 eyes had pathologic anterior segments and 3 eyes had glaucoma. In the control group, 1 eye had pathologic anterior segment, 4 eyes had glaucoma, and 1 eye was vitrectomized.

between January 2011 and December 2018, 14 eyes (7.41%) of 13 patients were re-DMEK (interest group). In the interest group, Fuchs endothelial corneal dystrophy (FECD) was the main indication for primary DMEK (11 eyes, 78.6%). Patient baseline data and causes of failed primary DMEK graft are shown in Table 1. In eyes with primary graft failure, defined as the absence of corneal clearing ≤3 months after DMEK, re-DMEK was performed within 1 month of diagnosis (Figure 1A, D, and G); in eyes with late graft failure, the mean time between primary DMEK and re-DMEK was 30.8 (20.4) months. All eyes were pseudophakic at the time of re-DMEK surgery. For comparative analysis, we analyzed an age-matched control group of successful pseudophakic primary DMEK eyes (n = 18), with a similar proportion of FECD eyes (14 eyes, 77.8%) and a similar proportion of eyes with comorbidities (6 eyes, 33.3%; $P = .590$; Table 1).

• **DONOR TISSUE PROTOCOL:** Corneal donor tissues for primary and re-DMEK grafts were obtained from the Barcelona Tissue Eye Bank; graft endothelial cell density (ECD, cell/mm^2) was measured by specular microscopy (Cellcheck Plus; Konan Medical Inc, Fair Lawn, New Jersey, USA). In the interest group, the mean age of the primary DMEK graft donor was 70.2 (11.7) years, the median ECD was 2450.0 (344.0) cells/mm^2, and the mean death-to-use time was 12.2 (1.3) days. The mean age of the secondary DMEK graft donor was 65.6 (9.6) years, with a mean ECD of 2712.6 (293.8) cells/mm^2, and the median death-to-use time was 12.0 (2.0) days. In the control group, the mean donor age was 68.8 (7.4) years, the mean graft ECD was 2583.6 (157.8) cells/mm^2, and the mean death-to-use time was 12.3 (2.0) days. Differences in donor data (age, ECD, and death-to-use time) between the secondary DMEK grafts and the control grafts were not statistically significant ($P = .216$, .213, and .719, respectively).

• **REPEAT DMEK SURGERY:** All re-DMEK surgeries were performed as standalone procedures by an experienced corneal surgeon (J.G.) under local anesthesia. Instead of performing a descemetorhexis, the failed DMEK graft was removed from the recipient's posterior stroma using a

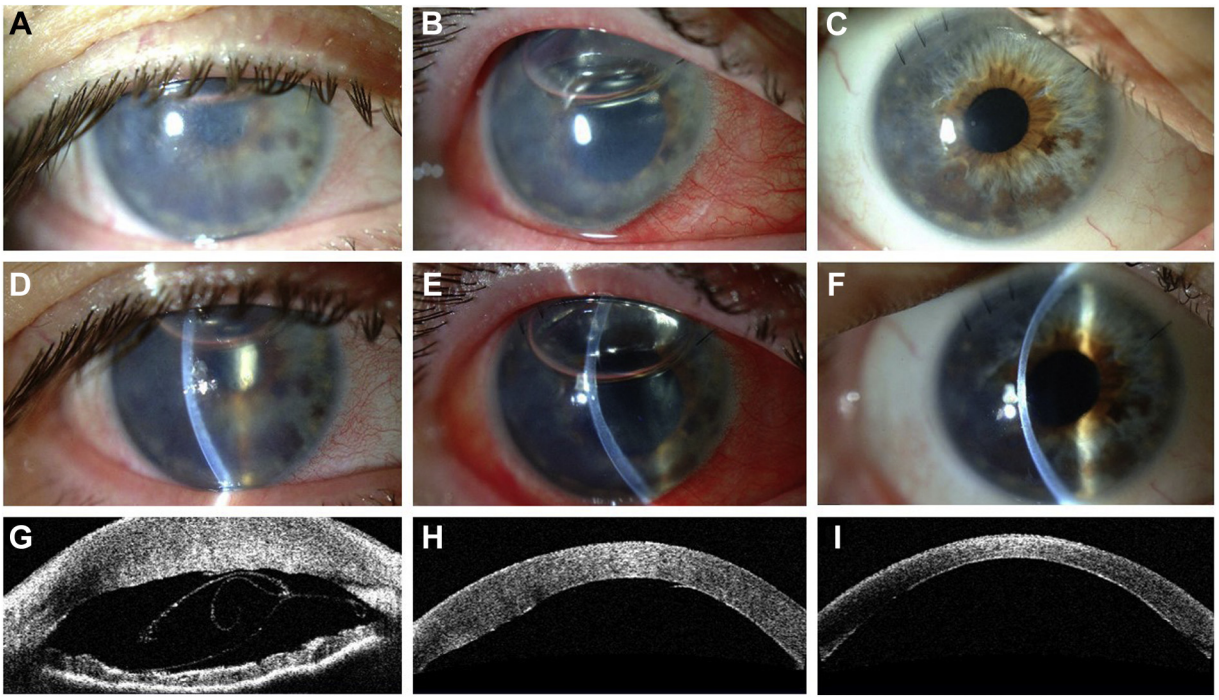


FIGURE 1. Case of successful repeat Descemet membrane endothelial keratoplasty (DMEK). A, D. Slit-lamp biomicroscopy showing corneal edema at day 5 after primary DMEK surgery; best-corrected visual acuity (BCVA) was 2.3 logMAR (Snellen 20/3990). B, E. Some corneal clearing was observed at day 2 after re-DMEK. C, F. Slit-lamp image showing corneal clearing 8 weeks after re-DMEK; at this stage, BCVA was 0.15 logMAR (Snellen equivalent 20/28), and this case reached 0 logMAR BCVA (Snellen equivalent 20/20) at 5 years of follow-up. G. Anterior segment optical coherence tomography (AS-OCT) (Visante OCT, Carl Zeiss, Oberkochen, Germany) showing complete graft detachment of the primary DMEK graft. H. AS-OCT showing attached re-DMEK graft and reduced corneal thickness. I. Attached re-DMEK graft and normal corneal thickness was seen on AS-OCT at 8 weeks of follow-up after re-DMEK.

reversed Sinskey hook and the DMEK forceps (P4818B; Duckworth & Kent, Baldock, United Kingdom) under air. A 3-mm limbal tunnel incision was reopened for insertion of the new DMEK graft. Donor Descemet roll was stained with trypan blue, configured into a "single" or "double roll," placed into an injector (Guell DMEK 2.2 injector, DK2200; Medicel, Thal, Switzerland), and injected into the recipient's anterior chamber while the anterior chamber maintainer kept intraocular pressure (IOP) at 5 mm Hg. Using indirect corneal manipulation under air and balanced salt solution, the new DMEK graft was gently unfolded, and positioning onto the recipient posterior stroma was performed using 20% sulfur hexachloride as tamponade, leaving a relatively soft eye at the end of the surgery. At the end of the surgery, subconjunctival methylprednisolone 1 mg/kg was administered.

• **POSTOPERATIVE PROTOCOL:** To ensure graft attachment with the aid of sulfur hexachloride 20% bubble, patients were instructed on different positioning regimens. Postoperative treatment consisted of topical tobramycin 0.3% and dexamethasone 0.1% (Tobradex; Alcon Cusi, El Mas Nou, Barcelona, Spain) 4 times daily for 4 weeks and tapering over the following 3 months (reduction in 1 drop every 4 weeks); timolol 0.5% (Cusimolol; Alcon Cusi) eye drops 2 times daily for 12 weeks, with additional ocular hypotensive medications if needed; and dexamethasone 0.05% and chloramphenicol 1% ointment at nighttime (DeIcol; Alcon Cusi) for 6 months, and then stopped in the absence of any inflammatory signs or signs of rejection. Oral methylprednisolone (Urbason; Sanofi Aventis Pharma SA, Barcelona, Spain) was also prescribed and slowly tapered off for the first 3 weeks: 40 mg/day for 3 days; 20 mg/day for 3 more days; 10 mg/day for 1 week; and 10 mg every 48 h for 1 week.

• **DATA COLLECTION:** Eyes were analyzed before re-DMEK, at months 3 (M3) and 6 (M6) after surgery, and at last postoperative observation; in eyes with postoperative follow-up ≥12 months (M12), this time point was also analyzed (M12). Best-corrected visual acuity (BCVA; logarithm of minimal angle of resolution [logMAR]) was measured using Snellen visual acuity projection charts. Eyes with failed re-DMEK grafts were excluded from the BCVA comparison analysis.

The primary endpoint was improvement in BCVA (ΔBCVA) at last follow-up observation compared with baseline (before the first DMEK surgery). Secondary

TABLE 2. Visual Outcomes Following Repeat Descemet Membrane Endothelial Keratoplasty

Repeat DMEK Group		ΔBCVA from Baseline (logMAR)	*P* Value	ΔBCVA from Before Re-DMEK (logMAR)	*P* Value
3-month BCVA, logMAR	0.22 (0.26)	−0.29 (0.38)	.028[a]	−1.04 (0.55)	.001[a]
6-month BCVA, logMAR	0.19 (0.22)	−0.23 (0.34)	.023[a]	−1.09 (0.53)	.001[a]
12-month BCVA, logMAR	0.08 (0.15)	−0.41 (0.29)	.012[a]	−1.26 (0.52)	.012[a]
BCVA at last follow-up, logMAR	0.09 (0.26)	−0.32 (0.39)	.037[a]	−1.07 (0.55)	.003[a]

ΔBCVA = change in best-corrected visual acuity; BCVA = best-corrected visual acuity; DMEK = Descemet membrane endothelial keratoplasty; logMAR = logarithm of minimal angle of resolution. BCVA values are presented in logMAR as mean (SD) or as median (P75-P25).
[a]$P < .05$.

outcomes were ΔBCVA at M3, M6, and M12 postoperatively from baseline and from before re-DMEK; percentage of eyes with final BCVA ≤0.30 logMAR (Snellen equivalent ≥20/40), and the percentage of eyes with final BCVA ≤0.09 logMAR (Snellen equivalent ≥20/25); rebubbling rate; postoperative ECD measured by specular microscopy (TOPCON SP3000p; Topcon Corp, Tokyo, Japan) and percent endothelial cell loss (%ECL); rejection rate; and re-DMEK graft failure rate. Visual outcomes during the first postoperative year, %ECL, and complications (including rebubbling and rejection rates) were compared between patient groups.

• **STATISTICAL ANALYSIS:** Statistical analysis was performed using SPSS software (v 23.0; IBM Corp, Chicago, Illinois, USA). Quantitative variables were described as mean (standard deviation) or as median (P75-P25) depending on whether or not they a normal distribution, respectively. Parametric or nonparametric tests were applied depending on whether or not variables had a normal distribution, respectively. Categorical variables were described as absolute and relative frequencies. χ^2 or Fisher exact tests were applied for comparison between categorical variables. The level of significance α for the statistical analysis was 0.05.

RESULTS

• **FEASIBILITY OF REPEAT DMEK:** We found no special difficulties from a surgical point of view, and no major preoperative complications were observed (Figure 1B, E, H).

• **VISUAL ACUITY:** In the re-DMEK group, the mean baseline BCVA was 0.55 (0.42) logMAR (Snellen equivalent 20/71 [20/53]) and the median BCVA before re-DMEK was 1.30 (0.65) logMAR (Snellen equivalent 20/400 [20/89]). No re-DMEK grafts had primary graft failure, and none had failed at M3 (Figure 1C, F, I) and M6. Of the 9 re-DMEK eyes with postoperative follow-up ≥12 months, 1 graft had failed at 8-month follow-up and was excluded from the analysis. The mean baseline BCVA in the control group was 0.52 (0.40) logMAR (Snellen equivalent 20/60 [20/50]), which was not statistically significantly different from the baseline BCVA in the re-DMEK group ($P = .846$).

At last observation (mean follow-up time 14.5 [42.5] months), the mean final BCVA was 0.09 (0.26) logMAR (Snellen equivalent 20/25 [20/36]) in eyes with functional re-DMEK grafts (n = 11). The mean final ΔBCVA from baseline was statistically significant ($P = .037$), as well as from re-DMEK ($P = .003$). Visual results after re-DMEK are shown in Table 2. ΔBCVA was statistically significant from baseline and from before re-DMEK at all time points analyzed. Statistically significant ΔBCVA was noted from baseline to M3 ($P = .028$) and again between M6 and M12 ($P = .028$). Nine of 11 functional re-DMEK eyes (81.8%) reached final BCVA ≤0.30 logMAR (Snellen equivalent ≥20/40), and 6 eyes (54.5%) reached BCVA ≤0.09 logMAR (Snellen equivalent ≥20/25).

No statistically significant differences were observed between patient groups in postoperative BCVA at M3, M6, and M12 ($P = .397$, .468, and .647, respectively), in percent of eyes reaching BCVA ≤0.30 logMAR (Snellen equivalent ≥20/40) at M12 ($P = .326$) and in percent of eyes reaching BCVA ≤0.09 logMAR (Snellen equivalent ≥20/25) at M12 ($P = .793$). Comparison of visual outcomes between patient groups is presented in Table 3.

• **ENDOTHELIAL CELL COUNT:** Mean %ECL at M3 after re-DMEK was 36.4 (4.0) (mean ECD at 3.0 [1.0] months 1629.0 [319.6] cells/mm^2) and in the control group was 35.4 (14.3) (mean ECD at 3.2 [4.4] months 1724.8 [466.5] cells/mm^2). The difference in mean %ECL between patient groups was not statistically significant ($P = .886$).

In functional re-DMEK eyes with follow-up ≥12 months, the mean final %ECL was 48.2 (15.1) (mean ECD at 36.6 [19.7] months 1356.8 [398.2] cells/mm^2), and in the control group, the mean %ECL was 49.9 (12.4) (mean ECD at 39.7 [18.4] months 1301.4 [319.2] cells/mm^2). The difference in

TABLE 3. Comparison of Visual Outcomes Between Repeat Descemet Membrane Endothelial Keratoplasty and the Age-Matched Control Group of Successful Primary Descemet Membrane Endothelial Keratoplasty Eyes During the First Postoperative Year

Variable	Repeat DMEK Group	Control Group	*P* Value
3-Month BCVA, logMAR	0.22 (0.26)	0.22 (0.21)	.397
6-Month BCVA, logMAR	0.19 (0.22)	0.16 (0.26)	.468
12-Month BCVA, logMAR	0.08 (0.08)	0.07 (0.22)	.647
Percent of eyes with BCVA ≤0.30 logMAR (Snellen ≥20/40) at 12 months	100	88.9	.326
Percent of eyes with BCVA ≤0.09 logMAR (Snellen ≥20/25) at 12 months	54.5	55.6	.793

BCVA = best-corrected visual acuity; DMEK = Descemet membrane endothelial keratoplasty; logMAR = logarithm of minimal angle of resolution. BCVA values are presented in logMAR as mean (SD) or as median (P75-P25).

mean total %ECL between patient groups was not statistically significant ($P = .580$).

• **POSTOPERATIVE COMPLICATIONS:** Rebubbling rates for partial or graft detachment after re-DMEK (4 eyes, 28.6%) were statistically nondifferent compared with primary DMEK eyes (3 eyes, 16.7%; $P = .669$). Two of the re-DMEK eyes that needed rebubbling also needed rebubbling after primary DMEK surgery. One re-DMEK eye required rebubbling twice, whereas no control eyes required >1 rebubbling.

Six re-DMEK eyes (42.9%) had complications in the postoperative period. One re-DMEK eye (7.1%) had an intraocular pressure spike within the first postoperative week requiring anterior chamber paracentesis, and 2 control eyes (11.1%) had significant postoperative intraocular pressure elevation. Macular edema was observed in 1 eye in the control group (5.6%) and in 2 re-DMEK eyes (14.3%), 1 of which was transient and self-limited, while the other occurred in a diabetic patient at M6. Intraocular lens (IOL) opacification was observed 1 eye in the control group (5.6%) and in 1 re-DMEK eye (7.1%), which had IOL exchange at 11 months. Immune rejection episodes occurred in 1 control eye (5.6%), and in 2 re-DMEK eyes (14.3%) that ended in graft failure. The differences between patient groups regarding complications were not statistically significant for significant intraocular pressure elevations ($P = .702$), macular edema ($P = .692$), IOL opacification ($P =. 568$), and immune rejection episodes ($P = .401$).

• **REPEAT DMEK GRAFT FAILURE:** Graft failure occurred in 3 re-DMEK eyes (21.4%) (mean time to diagnosis of failure 35.4 [25.4] months), 1 within the first postoperative year. Causes of failure were immune rejection in 2 eyes and endothelial cell exhaustion in 1 eye (Figure 2). Two re-DMEK eyes had needed rebubbling for graft detachment. Two eyes had tertiary DMEK, and the final BCVA was 0.15 logMAR (Snellen equivalent 20/28) in one eye and 0.04 logMAR (Snellen equivalent 20/22) in the other. The third patient underwent PKP (an elderly patient who was unwilling to comply with post-DMEK head positioning), and final BCVA was 0.30 logMAR (Snellen equivalent 20/40).

DISCUSSION

IN OUR STUDY, SECONDARY DMEK WAS TECHNICALLY feasible in all eyes with failed primary DMEK grafts. It has been suggested that the risk of remnants of the primary graft may be increased compared with virgin eyes during descemetorhexis in primary DMEK surgery.[20] However, we had no cases of apparent graft remnants, by using a combination of a reverse Sinskey hook and forceps, which we find important to check under air for a proper visualization.

We have found that re-DMEK results in significant, early, and continuous visual improvement. Although one study did not corroborate such findings,[21] continuous improvement in BCVA has been shown to occur after endothelial keratoplasty,[2,23] presumably because of corneal tissue remodeling at the host–interface junction.[23] In addition, visual results during the first postoperative year were comparable to those of primary DMEK eyes, including the percent of eyes reaching higher levels of BCVA (BCVA ≤0.09 logMAR) at M12. Our results are similar to those of previous studies,[2,20] including one study comparing re-DMEK eyes with successful primary DMEK in the fellow eye,[19] and are slightly superior to findings from another study.[21]

Complication rates between re-DMEK and primary DMEK eyes were comparable in our study. However, re-DMEK eyes had a 21.4% graft failure rate, which is high compared with our failure rate after primary DMEK (7.4%). This suggests that secondary DMEK grafts may be at an increased risk of failure, but we consider that further, prospective studies are warranted to ascertain whether the risk of graft failure is higher in eyes with previously failed DMEK grafts. Also of note, we observed

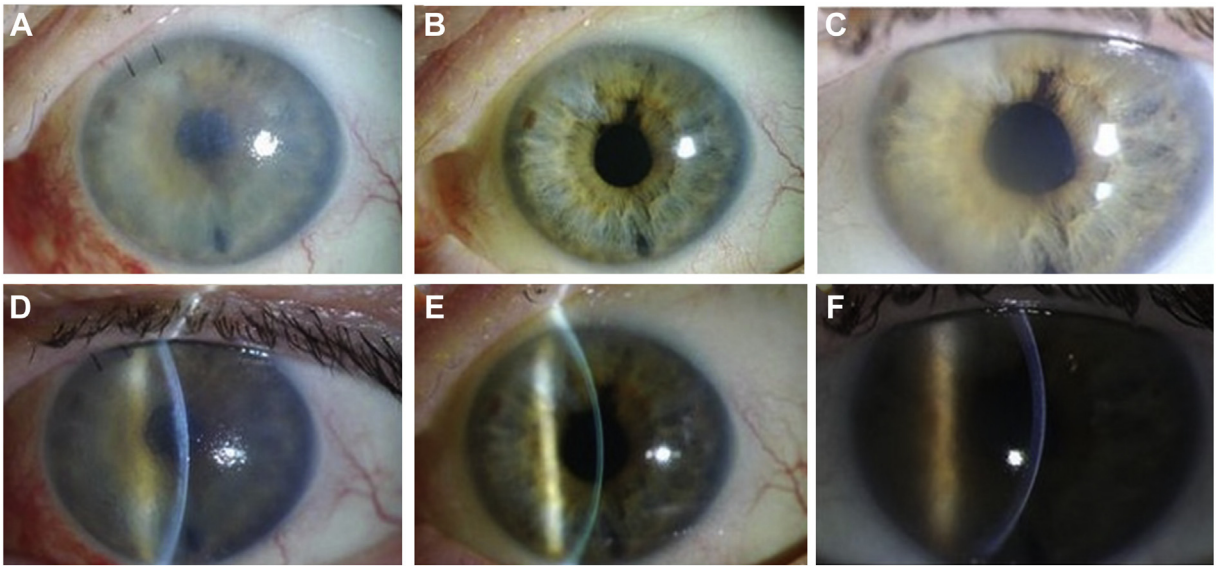


FIGURE 2. Clinical photographs of a case of failed repeat Descemet membrane endothelial keratoplasty (DMEK). A, D. Primary DMEK for Fuchs endothelial corneal dystrophy had primary graft failure. B, E. Complete corneal clearing 3 months after repeat DMEK. C, F. Late repeat DMEK graft failure because of endothelial cell exhaustion at 3.5 years of follow-up.

high rates of graft detachment requiring rebubbling in both patient groups, which were higher than our standard.[24] This may be because of the relatively high proportion of eyes with comorbidities in both groups in this study. Half of the re-DMEK eyes requiring rebubbling also needed rebubbling at the time of the first DMEK surgery; intrinsic host properties may contribute to graft adherence and influence the risk of graft failure.[23]

We found a relatively high rejection rate in re-DMEK eyes, although not statistically significantly different from the control group. One case without readily identifiable risk factors had a rejection episode 58 months after re-DMEK. Interestingly, the second case of re-DMEK graft rejection occurred in a patient who had primary DMEK for previously failed PKP and in whom the primary DMEK failed because of rejection. Our group has reported our experience with DMEK under failed PKP,[6] and we had documented no cases of immune rejection. However, this case raises the question of whether standard rejection protocols for DMEK suffice in eyes undergoing DMEK (both primary or re-DMEK) for previously failed PKP.

The main limitations of our study are the sample size and its retrospective nature, including the lack of structural analysis of the recipient cornea. Repeat endothelial keratoplasty has been shown to cause a decrease in corneal thickness, associated with increased visual acuity.[15,20,21,25,26] To overcome potential limitations regarding the control group, we analyzed eyes with clinically similar baseline characteristics and compared outcomes at similar time points after DMEK.

In conclusion, repeat DMEK for failed primary DMEK graft is a surgical feasible procedure that produces early and significant visual improvement. Although visual outcomes and rates of endothelial cell loss and complications are comparable to those of primary DMEK eyes, re-DMEK eyes may have a higher risk of graft failure. Larger, prospective studies of repeat DMEK are encouraged to ascertain differences in visual outcomes and complications between primary and re-DMEK, particularly the risks of allograft rejection and graft failure.

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Publication II

Secondary Endothelial Keratoplasty—A Narrative Review of the Outcomes of Secondary Corneal Endothelial Allografts

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Background. We review the literature on the efficacy and safety outcomes of secondary Descemet stripping endothelial keratoplasty (DSEK) and Descemet membrane endothelial keratoplasty (DMEK). **Methods.** Literature search of English-written publications up to September 27, 2020 in PubMed database, using the terms "endothelial keratoplasty" in combination with keywords "secondary" or "repeat." In addition, we manually searched the references of the primary articles. **Results.** Twenty-seven studies (n = 651 eyes) were retained and reviewed, including 10 studies on repeat DSEK, 8 studies on repeat DMEK, 6 studies of DMEK following DSEK, and 3 studies of DSEK after failed DMEK. All studies reported significant improvement in visual acuity after secondary endothelial keratoplasty (EK). Twelve studies compared visual outcomes between primary and secondary EK, reporting conflicting findings. Sixteen studies reported endothelial cell loss rates after secondary EK, and only 1 study reported significantly increased endothelial cell loss rates compared with primary EK. Allograft rejection episodes occurred in 1.8% of eyes (range, 0%–50%). Six studies compared complication rates between primary and secondary EK eyes, and only 1 study found a higher median number of complications. However, 2 studies reported higher regraft failure rates compared with primary EK eyes. **Conclusions.** Secondary EK is surgically feasible and renders significant visual improvement after failed primary EK, although it is not clear whether visual outcomes and allograft survival are comparable with primary EK, raising the question of whether secondary EK eyes are "low risk" as primary EK eyes. Further larger, prospective studies are encouraged to obtain additional quality data on secondary corneal endothelial allotransplantation.

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INTRODUCTION

Posterior lamellar keratoplasty, including Descemet stripping membrane endothelial keratoplasty (DSEK) and Descemet membrane endothelial keratoplasty (DMEK), has significantly progressed in the last decade, and endothelial keratoplasty (EK) techniques have superseded penetrating keratoplasty (PKP) as the corneal allograft transplantation techniques of choice in the management of corneal endothelial disease (Figure 1).[1-3] Primary or secondary corneal endothelial cell (CEC) failure is currently the main indication for corneal transplantation worldwide, representing 56% of all corneal transplants in the United States[2]; of these, 90% were EK grafts and only 10% were PKP grafts.[2] PKP may still be indicated in certain cases of primary or secondary corneal endothelial disease, particularly in eyes with significant corneal subepithelial or stromal scarring,

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Online Supplemental Appendix; http://links.lww.com/TP/C177 and Supplemental Glossary Terms; http://links.lww.com/TP/C233.

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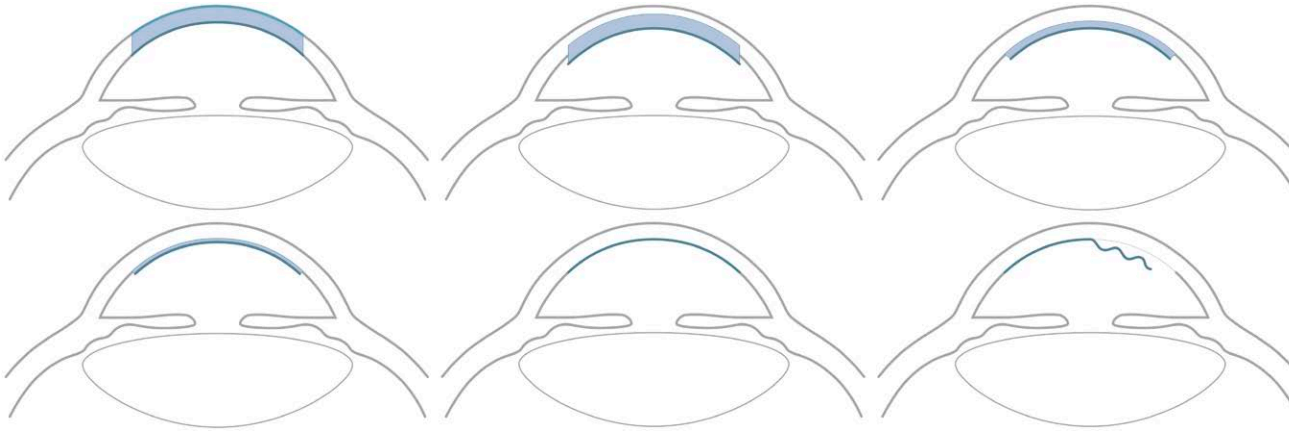


FIGURE 1. Schematic representation of the corneal allograft transplant procedures, including PKP and PLK techniques. In PKP (top left), the full-thickness of the recipient cornea composed of epithelium and Bowman's membrane (light green), corneal stroma (blue) and endothelial layer, and Descemet's membrane (dark green) is trephined and replaced by a full-thickness donor corneal allograft. In DLEK (top middle), an early PLK technique no longer in use, a posterior lamellar disc composed of endothelium, Descemet's membrane, and posterior stroma is manually dissected from the recipient cornea through a 9-mm sclerocorneal incision and replaced by an equally sized donor disc, placed against the recipient posterior cornea with an air bubble. In DSEK (top right), the EDM is stripped from the recipient cornea, and is replaced with a donor allograft composed of EDM, plus posterior stroma of variable thickness using a manual dissection or automatic dissection with a microkeratome (DSAEK). In ultrathin DSAEK (bottom left), the donor lenticule thickness is <100 μm owing to decreased stromal thickness, which may improve visual outcomes compared with the "conventional" DSEK techniques. In DMEK (bottom middle), the recipient's EDM complex is replaced only by donor Descemet's and endothelium. Donor lenticule grafts in DSEK and DMEK are positioned against the recipient's posterior stroma with air or with 20% sulfur hexafluoride and may be at risk of graft detachment (bottom right). DLEK, deep lamellar endothelial keratoplasty; DMEK, Descemet membrane endothelial keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty; DSEK, Descemet stripping endothelial keratoplasty; EDM, endothelial-Descemet's complex; PKP, penetrating keratoplasty; PLK, posterior lamellar keratoplasty.

where outcomes of EK may be suboptimal.[4] Although an increasing body of evidence favors DMEK over DSEK in terms of efficacy and safety,[5] DSEK may have a lower rate of rebubbling,[5] and is still the most performed EK surgery among corneal specialists worldwide.[2,6]

Graft Failure After Endothelial Keratoplasty

In contrast to other forms of allogeneic transplantation, primary corneal allografts are regarded as having high long-term success rates. However, graft failure is a potential complication following EK, as may occur after PKP grafts. The causes of failed EK grafts have been classified as either primary graft failure (PGF) or secondary graft failure. The most common cause of secondary graft failure is late endothelial graft failure (LEGF),[7,8] followed by immune rejection and glaucoma; other causes include infection, trauma, and epithelial ingrowth. The graft survival rate decreases with time, with reported mean survival rates after DMEK ranging from 83% to 96% at 5 y[9-11] and 79% at 10 y[11] and reported mean 5-y survival rates following DSEK ranging from 79.4% to 96% at 5 y.[12-15]

PGF has been defined as the absence of corneal clearing within 2 mo following EK. This may occur because of significant iatrogenic CEC loss during the preparation, insertion, or manipulation of the graft; because of "upside-down" graft (particularly during the early y of the technique or during the surgical learning curve) or because of graft detachment (GD). Reported rates of PGF ranges from 0% to 12.5% after DMEK,[8] 0%–29% after DSEK,[16] and 1.4% after ultrathin Descemet stripping automated endothelial keratoplasty (UT-DSAEK),[17] with a lower average PGF rate in favor of DMEK.[8] In the Cornea Preservation Time Study (CPTS), a benchmark study that analyzed the outcomes following DSEK, risk factors for primary or early failure following DSEK included patient-related factors (notably preoperative diagnosis of pseudophakic or aphakic corneal edema), donor-related factors (notably diabetes mellitus), and operative factors.[18]

GD occurs more commonly with DMEK compared with DSEK,[5,8] with mean reported rebubbling rates of 28.8% versus 14% in favor of DSEK.[8] Reported factors associated with decreased risk of GD following DMEK include increased surgeon experience, a larger descemetorhexis, the use of 20% sulfur hexafluoride (SF6) instead of air, a normal intraocular pressure (IOP), and a well-centered graft.[8,19,20] History of donor diabetes, increased prelamellar dissection central corneal thickness, and intraoperative complications have been identified as predictive factors for GD in the CPTS.[21] It has been suggested that GD is associated with increased EC loss following DSEK and therefore may decrease graft survival.[20] Rebubbling following GD achieves graft adhesion in a high percentage of patients in both DSEK and DMEK, but even in cases of successfully reattached grafts, 31%–35% of DSEK grafts still evolve to PGF.[22,23] Rebubbling for detached DMEK grafts has a definitive benefit and may allow similar visual outcomes as in uncomplicated DMEK and should usually be performed early.[24] However, the decision and timing of rebubbling for detached DMEK graft must be carefully considered, because prolonged air tamponade following rebubbling causes increased, IOP-independent CEC loss.[22,24,25]

Progressive CEC loss after EK is associated with reduced graft survival and LEGF. Following uncomplicated EK, the reported mean 6-mo endothelial cell loss rate (%ECL) ranges from 24% to 37% following DMEK, DSEK, or UT-DSAEK,[8-10,26,27] and the evidence of significant differences in %ECL between EK techniques is inconclusive.[25] The CEC loss after EK has a linear profile in the medium and long terms.[11,28] Mean rates of CEC loss after conventional DSEK/DSAEK range from 36% to 43% after

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3 y,[29] 48.7%–55% after 5 y[12,14,30] (comparable with UT-DSAEK[17]), and 71% after 10 y.[28] Rates of CEC loss after DMEK range from 48% to 59% at 5 y,[9,11,31] and 1 study reported a mean 68% EC loss at 10-y follow-up.[11] The cumulative probability of LEGF after DSEK was 1.3% at 3 y in the CPTS,[32] and the cumulative probability of survival at 5 y ranges from 79.4% to 96%.[12-15] The average rate of LEGF after DMEK (follow-up times between 6 mo and 8 y) is 2.2%,[8] with 1 study reporting a 6% rate of LEGF at 10-y follow-up,[11] and the graft 5-y survival probability ranges from 83% to 96%.[9-11] Compared with PKP grafting, the CEC loss rate following EK is higher in the first 6–12 mo postoperative, mostly due to manipulation of the graft during surgery. However, the CEC loss is comparable between EK and PKP after 3 y of follow-up,[33] and over the long term, the CEC loss in PKP grafts is greater than with EK grafts. In the Cornea Donor Study, a benchmark study reporting outcomes following PKP, the median CEC loss rates at 5- and 10-y follow-up after PKP were 69%–75% (in contrast with 48%–59% after EK) and 76% to 79% (versus 68–71% for EK), respectively.[34,35]

EK is regarded as a low-risk setting for allograft rejection episodes, with significantly lower rejection rates compared with PKP.[8,16,36] Mean rejection rates are 10% (range, 0%–45%) following DSEK (follow-up times between 6 mo and 8 y)[8] and 1.9% (range, 0%–5.9%) after DMEK (follow-up times between 6 mo and 10 y)[8,11]; the 5-y risk of rejection after DMEK may be as much as 71% lower than for DSEK.[31] The 5-y cumulative probability of rejection episodes after UT-DSAEK was 6.9%.[17] The rejection rates following EK grafting are significantly lower compared with those of PKP, in which overall 30% may experience at least 1 episode of immune reaction.[37] We refer the reader to a comprehensive review on the immune mechanisms after modern lamellar keratoplasty for further detail on the clinical and pathogenic mechanisms involved in corneal allograft rejection.[38]

Rejection episodes may be a predictive factor for graft failure or need of graft exchange after EK,[15,39,40] although this is not consensual.[31,41] In the setting of PKP, about one-third of grafts with history of at least 1 episode of allograft rejection will eventually fail.[37] There is significant variation in the reported risk of graft failure after immune rejection after DSEK. In the CPTS, the cumulative probability of rejection was 3.6% 3 y after DSEK, and 27% of eyes with definite graft rejection subsequently failed.[39]

Secondary Endothelial Keratoplasty

Repeat keratoplasty has become an increasing indication for corneal transplantation, being the fourth most frequent indication in the United States (13% of all corneal transplant procedures performed in 2019).[2] Repeat keratoplasty has a long track record of safety and efficacy in eyes with previously failed PKP grafts (repeat PKP),[42] but secondary PKP grafts are considered high-risk cases because of increased risk of rejection and failure. In the Collaborative Corneal Transplantation Studies, a benchmark study in the field of corneal allogeneic transplantation, the number of previous PKP grafts was a strong risk factor for graft failure, with a 1.2-fold increased risk with each additional graft.[43] Five-year graft survival after primary PKP is 92%–95% and decreases sequentially with each regraft (79%–82% after secondary graft, 54%–71% after tertiary graft, and 42%–56% after ≥4 grafts).[6,44] Allograft rejection after PKP occurs earlier with a more fulminant course in regrafts that in primary grafts, and the risk of regraft failure is especially high if previous graft failure was a result of an allograft rejection.[45]A number of factors contribute to increased risk of immunological rejection in the setting of repeat PKP allografts,[46] including previous alloimmune response (regraft-associated sensitization) and residua of the previous surgery such as corneal neovascularization and peripheral anterior synechiae.[4]

EK is becoming increasingly indicated in retransplantation, with estimated regraft rates of 10% in the United States and 14% worldwide.[2] In the setting of failed primary PKP graft, EK has proven to be a safe and effective technique.[47-53] A recent meta-analysis found that eyes undergoing EK for failed PKP graft had a significantly lower risk of graft rejection compared with eyes undergoing repeat PKP.[54] In our cohort of eyes undergoing DMEK after failed PKP graft,[51] we found a significant improvement in visual acuity and a high rate of clear corneal grafts at 2-y follow-up; we have however recently documented 1 case of DMEK graft rejection failure after PKP, which ended in graft failure requiring repeat DMEK.[55]

In eyes with failed primary EK grafts or cases of "suboptimal DSEK" (DSEK eyes with poor visual outcomes), secondary EK has been proposed as a potentially safe and effective strategy. Zafar et al[56] have reported an overall probability of receiving a repeat EK of 6.1% at 6 mo and 16.9% at 8 y. In this large retrospective study, younger age, male gender, Asian or melanodermic ethnicity, glaucoma diagnosis, prior or concurrent glaucoma surgery, macular pathology, prior anterior segment surgeries, and lower surgeon volume were found to be factors associated with increased risk of repeat EK.[56] Regrafts were also at increased risk of repeat EK in their study.[56]

In this study, we provide a qualitative literature review on the techniques, efficacy, and safety of secondary EK.

MATERIALS AND METHODS

We conducted a literature search in the PubMed database to assess the functional outcomes following secondary EK. We searched English-written publications up to September 27, 2020, using the following query: "Endothelial keratoplasty"[Title/Abstract] AND ("secondary"[Title/Abstract] OR "repeat"[Title/Abstract]). To reduce the chance of missing relevant articles, we searched manually the references of the primary articles. We included case reports, case-control, cross-sectional, retrospective, or prospective studies, including studies in which the patient groups included EK and PKP eyes, in which we analyzed the secondary EK eye group only. We excluded studies in which the aim of the study was not assessing functional outcomes (visual acuity, graft failure). We also excluded studies of secondary EK for previously failed deep lamellar EK, as this technique has been superseded by DSEK and DMEK. After removing duplicate records, we independently screened the titles, abstract, and keywords to identify relevant articles in secondary EK (DSEK/DSAEK or DMEK). Studies not related to secondary DSEK or secondary DMEK were excluded.

We performed a qualitative analysis of the full-text articles assessed. We assessed 358 articles for eligibility (356

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from PubMed database and 2 articles by manual search of primary articles) and selected all the original studies (case reports, case series, and comparative studies) that reported the results following secondary EK to include in the analysis. We excluded conference abstracts, editorials and letters to the editor, irrelevant records, nonhuman studies, and review articles. We independently extracted data into a customized database. We analyzed the outcomes of secondary EK according to type of primary and secondary EK surgeries (repeat DSEK, repeat DMEK, DMEK after failed primary DSEK, and DSEK after failed primary DMEK). The extracted information included authors of the study, publication year and journal, sample size (number of eyes), indication for secondary EK and proportion of eyes undergoing primary EK for Fuchs endothelial corneal dystrophy, time between primary and secondary grafts, preoperative corrected distance visual acuity (CDVA), postoperative follow-up time, and final CDVA. When reported, we also extracted information regarding the surgical technique, %ECL, complication rates (rebubbling for GD, allograft rejection, other complications), and rate of regraft failure.

RESULTS

We found 27 studies reporting outcomes following secondary EK (n = 651 eyes). The study by Yazu et al[57] was excluded because visual outcomes were not reported following repeat DSEK. We excluded the studies by Dirisamer et al[58] and by Kim et al[59] because they reported outcomes of DSEK after failed deep lamellar EK, an earlier technique of corneal endothelial transplantation which has fallen into disuse. Finally, we excluded the study by Agha et al[60] because the same group had published 2 different comparative case series on repeat DMEK and repeat DSAEK in the same year with larger cohorts.

Repeat DSEK

Ten studies (n = 403 eyes) analyzed the outcomes of repeat DSEK (re-DSEK).[61-70] The 2 main indications for re-DSEK were failed primary DSEK graft and poor visual performance after primary DSEK. Prior aqueous shunt surgery, donor graft CEC density, and at least 1 documented postoperative rejection episode were the main factors associated with the need for DSEK graft exchange after primary DSEK in a multivariable model.[40]

Two re-DSEK studies included eyes with suboptimal primary DSEK64,67; the proportion of eyes that had re-DSEK for this indication was highly variable, ranging from 1.9% to 76% (Table 1).[63,66] Even in eyes with clear primary DSEK grafts, final CDVA is variable, with a mean postoperative CDVA of 20/40–20/30 at 3–6 mo following DSEK or ultrathin DSEK (UT-DSEK), and % eyes reaching CDVA ≥20/40 ranging from 38% to 100%.[16,71] In addition, the proportion of eyes reaching CDVA ≥20/25 following DSEK was relatively low (6%–31%). Poor visual recovery after primary DSEK can occur in eyes with clear grafts due to interface abnormalities or significant wrinkles and folds in the pupillary area.[63] The latter has been hypothesized to be the result of mismatch between donor and recipient corneal curvatures.[63] Proposed abnormalities contributing to poorer visual performance following DSEK include increased corneal aberrations of the posterior surface,[72,73] and increased light scattering at the host-donor interface, which may be due to host Descemet's membrane (DM) remnants, presence of interface material such as fibrocellular tissue including cytokeratin, fibronectin, and vimentin,[74] or stromal contraction of the donor graft.[75] Graft thickness is likely to influence visual outcomes following DSEK, and this has been one argument favoring UT-DSEK over conventional DSEK27; however, this remains controversial.[76] Interestingly, DMEK has been demonstrated to result in fewer posterior corneal aberrations compared with conventional DSEK and UT-DSEK.[73,77]

Repeat DSEK can be performed under sub-Tenon or retrobulbar anesthesia supplemented with neuroleptic anesthesia. Repeat DSEK is performed through the same incision site as the primary DSEK procedure by opening the original incision with a keratome. The failed DSEK donor graft can be removed using a reverse Sinskey hook to detach it from the recipient corneal stroma engaging the edge of the graft[63,64] or alternatively using a bent 27-gauge needle inserted through the limbus at the 12-o'clock position,[66] and then removed from the anterior chamber (AC) using an intraocular forceps. It is important to make sure the graft has not adhered to the iris, as these adhesions may be quite dense with thick membranes that may lead to iris dehiscence upon graft removal.[78] The new donor graft is prepared as for standard primary DSEK or UT-DSEK, but the lenticule diameter should be the same or slightly larger than the previous failed DSEK graft. The lenticule insertion and AC filling techniques are the same as for the primary DSEK procedure.[64,66] Interestingly, secondary DSAEK has anecdotally been performed without removal of the failed DSAEK graft in a recent case report, with successful improvement of pain and corneal edema in a painful red eye with bullous keratopathy and poor vision.[79] Matsumoto et al[69] have reported repeat DSAEK to render successful anatomical and functional results in combination with phakic intraocular lens (IOL) explantation and cataract surgery.

The standard postoperative regimens following re-DSEK include topical tobramycin 0.3% eye drops for 4 wk; proposed topical corticosteroid regimen varies between surgeons, but maintenance therapy with a topical steroid over a long period is a common aspect.[64,66] Systemic prednisolone (1.5 mg/kg body weight with tapering over 3 mo) has been considered in cases of DSEK failure due to allograft rejection.[66]

Most eyes can expect clear functioning and improvement in CDVA following re-DSEK. CDVA improved in 97% of eyes that underwent re-DSEK for poor visual performance.[63] Reported visual outcomes seem to be similar to those achieved for primary DSEK surgery,[67] with mean CDVA after re-DSEK ranging from 0.50 to 0.18 logMAR (Snellen equivalent 20/30–20/63).[63,64,66,70] Besides, maximal postoperative CDVA after re-DSEK reported rates of eyes reaching CDVA ≥20/40 following re-DSEK ranges from 20% to 100%.[62-64] If studies with ≤2 eyes were excluded from this analysis, then the proportion of eyes reaching CDVA ≥20/40 would be 20%–82%, and no studies observed eyes reaching CDVA ≥20/25.[62] Visual results in these eyes are negatively influenced by high-order aberrations of the posterior corneal surface[57] and positively influenced by a higher preoperative IOP before re-DSEK.[68]

Rates of CEC loss were reported in 3 studies (n = 192 eyes), ranging from 36.7% to 47.3% (follow-up times

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TABLE 1.

Outcomes of repeat DSEK reported in the literature

Author	Journal (mo/y)	Eyes (n)	Patient age (y)	Fuchs indication for primary EK (%)	Cause of re-DSAEK	Ocular comorbidities (%)	Time between primary DSAEK and re-DSAEK (mo)	F-U time after repeat DSAEK (mo)	CDVA before re-DSAEK	Mean preoperative CCT (μm)	CDVA after re-DSAEK	% Eyes reaching CDVA ≥20/40	%ECL	Mean final CCT (μm)	Rebubbling rate (%)	Rejection rate (%)	Graft failure rate (%)	Comments
Gorovoy et al[61]	*Cornea* (Feb/2008)	2	59.5 ± 9.5	100%	Rej (50%)/late endothelial failure (50%)	50%	20 ± 7	6	0.80 ± 0.20 logMAR	Patient 2=875μm	0.20 ± 0.10 logMAR	100%	N/R	Patient 2 = 625 μm	0%	50%	0%	No signs of interface scarring after failed graft removal
Lee et al[62]	*Cornea* (Jun/2009)	5	68.4 ± 6.6	40%	Dislocated graft (40%)/iatrogenic PGF (60%)	60%	3.2 ± 2.7	7.6 ± 3.7	N/R	N/R	0.85 ± 0.62 logMAR	20%	N/R	638.5 ± 31.4 μm	0%	0%	20%	One patient experienced primary graft failure
Letko et al[63]	*Ophthalmology* (Feb/2011)	37	69.0 ± 12.0	86%	Unsatisfactory visual outcome (76%)/endothelial decompensation (24%)	24.3%	11/13	N/R	Snellen 20/60/ counting fingers	809/787	Snellen 20/30/ Snellen 20/60	82%	N/R	678/666	N/R	N/R	N/R	Improved visual acuity in 97% of eyes
Kim et al[64]	*Cornea* (Oct/2012)	20	69.9 ± 11.9	55%	PGF (40%)/Rej (20%)/ endothelial failure (40%)	15%	13.1 ± 10.3	27.0 ± 13.4	1.76 ± 0.62 logMAR	N/R	0.50 ± 0.41 logMAR	59%	47.3% (final F-U)	N/R	5%	0%	0%	IOP change non-significant; in eyes without comorbidities, mean CDVA improved to 0.37 logMAR
Ghosh et al[65]	*Clin Ophthalmol* (May/2013)	1	77	100%	Epithelial ingrowth	Dry AMD	22	18	1.0 logMAR	N/R	0.10 logMAR	100%	N/R	N/R	0%	0%	0%	Careful stripping and cleaning of the interface to remove any epithelial cells in cases of epithelial ingrowth after DSEK in warranted
Nahum et al[66]	*Cornea* (May/2016)	51	69.6 ± 13.1	39.1%	Rej (29.4%)/EC exhaustion (68.6%)/interface abnormalities (1.9%)	31.3%	26.4 ± 22.8	21.2 ± 17.4	1.38 ± 0.60 logMAR	N/R	0.34 ± 0.49 logMAR	N/R	44% ± 21% (2-y F-U)	N/R	0%	0%	9.8%	Visual outcomes between re-DSAEK and primary DSAEK were similar

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TABLE 1. (Continued)

Author	Journal (mo/y)	Eyes (n)	Patient age (y)	Fuchs indication for primary EK (%)	Cause of re-DSAEK	Ocular comorbidities (%)	Time between primary DSAEK and re-DSAEK (mo)	F-U time after repeat DSAEK (mos)	CDVA before re-DSAEK	Mean preoperative CCT (μm)	CDVA after re-DSAEK	% Eyes reaching CDVA ≥20/40	%ECL	Mean final CCT (μm)	Rebubbling rate (%)	Rejection rate (%)	Graft failure rate (%)	Comments
Dickman et al[67]	*Am J Ophthalmol* (Sep/2018)	103	70 ± 9	42%	PGF (25%)/endothelial failure (50%)/Rej (17%)/others (9%)	N/R	N/R	24	1.46 ± 0.10 logMAR	N/R	0.57 ± 0.09 logMAR	N/R	N/R	N/R	N/R	N/R	9% at 2y	81% cumulative probability of 5-y regraft survival
Thompson et al[68]	*Cornea* (Feb/2019)	121	70 ± 12	33%	PGF (30.6%)/ Rej (5.6%)/ late endothelial failure (58%)/ others (5.8%)	Glaucoma (36%)	23.2 ± 22.3	12	1.54 ± 0.79 logMAR	673 ± 117	0.65 ± 0.62 logMAR	N/R	36.7% (6-mo F-U)	N/R	15%	N/R	N/R	Higher preoperative IOP was predictive of greater improvement in CDVA after re-DSEK; glaucoma and previous PKP were not predictive of visual outcomes
Matsumoto et al[69]	*JCRS Online Case Reports* (Oct/2019)	1	55	0%	Late endothelial failure (100%)	Phakic IOL (100%)	24	6	2.0 logMAR	N/R	0.0 logMAR	100%	N/R	614 μm	0%	0%	0%	Repeat DSAEK was performed in combination with phakic IOL explantation and cataract surgery
Kaur et al[70]	*Indian J Ophthalmol* (Oct/2019)	62	52.6 ± 17.1	29%	PGF (55%)/Rej (16%)/endothelial failure (29%)	25.8%	8 (range, 0.15–19)	12	N/R	732.8 ± 82.5	0.44 ± 0.25 logMAR	N/R	N/R	688.3 ± 110.9	N/R	N/R	13%	87% of eyes with clear grafts at postoperative y 1

AMD, age-related macular degeneration; CCT, corneal central thickness; CDVA, corrected distance visual acuity; DSAEK, Descemet stripping automated endothelial keratoplasty; DSEK, Descemet stripping endothelial keratoplasty; EC, endothelial cell; %ECL, endothelial cell loss rate; EK, endothelial keratoplasty; F-U, follow-up time; IOL, intraocular lens; IOP, intraocular pressure; N/R, not reported; PGF, primary graft failure; PKP, penetrating keratoplasty; re-DSAEK, repeat DSAEK; re-DSEK, repeat DSEK; Rej, rejection.

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ranging from 12 to 27 mo).[64,66,67] Only 1 study compared %ECL between primary DSEK and re-DSEK eyes and found no statistically significant differences.[66] However, 1 study suggests that their re-DSEK cohort had accelerated %ECL compared with their previously published data on primary DSEK eyes.[64]

Rebubbling rates were reported in 5 studies and ranged from 0% to 15%. [61,64-66,68] Immune rejection episodes were reported in 4 studies (n = 54 eyes),[61,64-66] and only occurred in 1 study (1 eye, 1.9%), which required continued topical steroid therapy for recurrent keratic precipitates.[61] Regraft failure rates were reported in 8 studies (n = 245 eyes), ranging from 0% to 20% (follow-up times ranging from 6 to 27 mo).[61,64-67,70] A prospective long-term analysis performed by the Netherlands Organ Transplantation Registry found that regraft survival is lower compared with primary graft survival.[67] These findings are similar to those reported in a retrospective study in which re-DSEK grafts were reported to be at increased risk of rejection and graft failure compared with primary DSEK eyes (Moura-Coelho et al, personal communication, 2019).

Repeat DMEK

Eight publications (n = 130 eyes) analyzed the outcomes of repeat DMEK (re-DMEK) for failed primary DMEK graft (Table 2).[55,80-86] Excluding the case report by Alió del Barrio et al,[84] primary DMEK was performed for Fuchs endothelial corneal dystrophy in 78.6%–100% of cases. Histopathological analysis of failed primary DMEK grafts has shown that the majority of failed primary DMEK grafts have subclinical, preoperative corneal endothelial dysfunction and that most cases have an abnormal fibrillary posterior collagenous layer.[81,87] DMEK failure may be associated with innate immune activation and increased cytokine levels in the aqueous humor, particularly interleukins 5 and 8.[86]

Regrafting has rendered a surgically feasible approach in cases of failed primary DMEK. Compared with primary DMEK, certain particularities in the operative protocol must be considered in re-DMEK.[55,82] The previous 3.0-mm corneal tunnel incision is reopened, the failed DMEK graft is disinserted from the host stroma using a reverse Sinskey hook under air, and the graft is removed with a DMEK forceps.[55] At this stage, careful removal of graft remnants by scraping can be performed while avoiding damage to the host posterior stroma[55,82]; injecting trypan blue into the AC may aid in visualizing DM remnants.[82] Donor Descemet roll preparation, insertion, positioning, and tamponade into the host posterior stroma are performed as for primary DMEK surgery; 20% SF6 may be used as tamponade, leaving a relatively soft eye at the end of the surgery.[55] Particularly in cases when re-DMEK is performed to manage GD, leaving the host AC completely filled with air for 60–120 min can help in reducing the risk of detachment occurring in the same quadrants, and then air-liquid exchange is performed to leave a 30%–50% air bubble.[82] It has been reported anecdotally that a second DMEK graft without removal of the failed DMEK graft effectively restored corneal transparency and vision in a case of pseudophakic bullous keratopathy.[84] Reported postoperative medication regimens are usually the same as for primary DMEK surgery.[55,82,83] We routinely prescribe topical tobramycin 0.3% and dexamethasone 0.1% eye drops every 2 h in the first postoperative day, then 6 times a day for the first postoperative week, then 4 times a day for 4 wk, and then tapering the topical steroids over the following 3 mo; topical dexamethasone 0.05% and chloramphenicol 1% ointment at bedtime for 12 wk and then at bedtime 3 times weekly until the sixth postoperative month, with discontinuation in the absence of any inflammatory signs or symptoms of rejection; and topical ocular hypotensive medications over 3 mo. In addition, we prescribe oral methylprednisolone 40 mg/d for 3 d, followed by tapering over the first 3 postoperative wk.[55]

Mean/median follow-up periods after re-DMEK ranged from 3.3 to 18 mo (range, 3–89 mo).[55,79-83,85,86] Reported mean final CDVA following re-DMEK ranged from 0.33 to 0.09 logMAR (Snellen equivalent 20/25–20/43). Five studies (n = 105 eyes) reported the proportion of eyes reaching higher CDVA at final observation[55,81-84]: 82%–100% of eyes reached CDVA ≥20/40, and 13.3%–81% of eyes reached CDVA ≥20/25. Three of these studies (n = 86 eyes) additionally reported that 18.2%–61% of eyes reached final CDVA ≥20/20.[55,82,83] The changes in corneal pachymetry were reported in 6 studies (n = 110 eyes).[81-86] Mean central corneal thickness before re-DMEK ranged from 631 to 931 μm and decreased to 512–576 μm at 6- to 12-mo follow-up after re-DMEK.

All studies except the case report by Alió del Barrio et al[84] reported comparative analyses between primary and re-DMEK eyes (n = 129 re-DMEK eyes): 1 study (n = 6 eyes) compared the preoperative and postoperative CDVA after the first and the second DMEK grafts[80]; 2 studies compared re-DMEK eyes with the subgroup of patients with successful fellow-eye primary grafts (n = 38 eyes)[81,83]; and 4 were retrospective, comparative case series (n = 50 eyes).[55,82,85,86] Five studies (n = 68 eyes) reported that visual outcomes were comparable between primary and re-DMEK eyes,[55,80,83,85] including the percentage of eyes that reached higher levels of CDVA at 1-y comparisons.[55,83] However, 2 studies reported inferior visual outcomes after re-DMEK compared with primary DMEK.[81,82] The time between graft failure and regrafting may influence visual outcomes, because average intervals between PGF or GD and regrafting ranged from 9 d and 2.9 mo in the series reporting comparable visual outcomes,[55,80,83] contrasting with the 2 studies reporting inferior visual outcomes, in which average times ranged from 146 d to 16 mo.[81,82] Prompt regrafting minimizes the duration of host corneal decompensation and associated stromal changes,[82,83,85] which can lead to increased backscatter.[60]

Mean %ECL following re-DMEK was reported in 6 studies (n = 123 eyes),[55,81-83,85] ranging from 29.8% to 49.5% at 6-mo follow-up,[82,83,85,86] from 34% to 49.8% at 12-mo follow-up,[81,83,86] and 48.2% in eyes with medium-term follow-up.[55] Six studies (n = 111 eyes) reported rebubbling rates following re-DMEK, ranging from 5.9% to 33% after excluding the case report by Alió del Barrio et al.[55,80,82,83,85,86] Eyes that had GD after primary DMEK may be at increased risk of rebubbling after re-DMEK,[55,82] which suggests that host intrinsic properties may interfere with graft adherence. Four studies (n = 104 eyes) reported rejection rates,[55,81-85] ranging from 0% to 14.3%.[55,81-83] In the studies reporting eyes with immune rejection episodes in the regraft, 1 eye of each cohort had undergone

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TABLE 2.

Outcomes of repeat DMEK

Author	Journal (mo/y)	Eyes (n)	Patient age (y)	Fuchs indication for primary EK (%)	Cause of re-DMEK	Ocular comorbidities (%)	Time between primary DMEK and re-DMEK (mo)	F-U time after re-DMEK (mo)	CDVA before re-DMEK	Mean preoperative CCT (μm)	CDVA after re-DMEK	% Eyes reaching CDVA ≥20/40	%ECL	Mean final CCT (μm)	Rebubbling rate (%)	Rejection rate (%)	Graft failure rate (%)	Comments
Yoeruek et al[80]	*Cornea* (Nov/2013)	6	66.8 ± 5.6	100%	Failed primary DMEK (unspecified)	0%	2.9 ± 1.5	3.3 ± 1.7	1.50 ± 0.28 logMAR	N/R	0.13 ± 0.05 logMAR	N/R	N/R	N/R	33.3%	N/R	0%	Visual outcomes and types of complications and their incidence were comparable with the first surgery
Cirkovic et al[81]	*Cornea* (Jan/2015)	18	69.0 ± 7.0	83.3%	Failed primary DMEK (78%)/graft detachment not resolved by rebubbling (22%)	17%	4.9	12	1.90 logMAR	807 ± 160	0.3 logMAR	86.7%	45% ± 11% (12-mo F-U)	576 ± 178	0.5 ± 0.9 rebubbling procedures	0%	5.6%	Telephone interviews indicative of a very strong recommendation for repeat DMEK
Baydoun et al[82]	*Ophthalmology* (Jan/2015)	17	69 ± 14	88.2%	Graft detachment (82%)/EC exhaustion (12%)/Rej (6%)	0%	16 ± 9	12	N/R	703 ± 26	86% CDVA ≥20/40, and 57% CDVA ≥20/25	86%	49.8% (12-mo F-U)	515 ± 39	5.9%	5.9%	17.6%	Increased %ECL and lower % eyes with CDVA ≥20/25 compared with primary DMEK eyes
Price et al[83]	*Ophthalmology* (Aug/2015)	55	69 (range, 42–89)	93%	Surgical complications (38%)/PGF (40%)/EC exhaustion (9%)/other causes (13%)	11%	21 d in surgical complications/32 d in PGF/27 mo in EC exhaustion	18 (range, 3–61)	N/R	631 ± 81	20/25 Snellen	100%	31 ± 14% (12-mo F-U)	512 ± 40	13%	0%	2%	Re-DMEK eyes had similar %ECL and visual outcomes compared with fellow primary DMEK eyes
Alió del Barrio et al[84]	*Cornea* (Jun/2018)	1	72	0%	Rej (100%)	100%	18	6	0.70 logMAR	691 μm	0.25 logMAR	100%	N/R	529 μm	0%	0%	0%	Repeat DMEK was successful without primary DMEK graft removal (DMEK under failed DMEK)

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TABLE 2. (Continued)

Author	Journal (mo/y)	Eyes (n)	Patient age (y)	Fuchs indication for primary EK (%)	Cause of re-DMEK	Ocular comorbidities (%)	Time between primary DMEK and re-DMEK (mo)	F-U time after re-DMEK (mo)	CDVA before re-DMEK	Mean preoperative CCT (μm)	CDVA after re-DMEK	% Eyes reaching CDVA ≥20/40	%ECL	Mean final CCT (μm)	Rebubbling rate (%)	Rejection rate (%)	Graft failure rate (%)	Comments
Agha et al[85]	*Clin Ophthalmol* (Mar/2019)	13	73.2 ± 7.6	84.6%	Failed primary DMEK (unspecified)	23.1%	12.5 ± 6.0	6	1.96 ± 0.99 logMAR	929 ± 217	0.33 ± 0.20 logMAR	N/R	30.1% (6-mo F-U)	519 ± 43	23.1%	0%	0%	Functional and anatomical outcomes were similar between re-DMEK and primary DMEK eyes
Luznik et al[86]	*Ophthalmology* (Oct/2019)	6	72 ±11	83.3%	Failed primary DMEK (unspecified)	N/R	18.5	12	1.50 (range, 0.4–2.0) logMAR	931 ± 245 μm	0.3 (range, –0.2 to 0.8) logMAR	N/R	49.0 ± 8.8% (12-mo F-U)	524 μm	16.7%	0%	16.7% (PGF)	Increased complication rates and levels of cytokines in the aqueous humor compared with primary DMEK eyes,
Moura-Coelho et al[55]	*Am J Ophthalmol* (Mar/2020)	14	68.4 ± 9.0	78.6%	PGF (57%)/EC exhaustion (29%)/Rej (14%)	35.7%	Eyes with PGF within 30 d; eyes with late graft failure 30.8 ± 20.4 mo	14.5 (range, 6–89)	1.30 ± 0.65 logMAR	N/R	0.09 ± 0.26 logMAR	81.8%	48.2 ± 15.1% (final F-U)	N/R	28.6%	14.3%	21.4%	Re-DMEK eyes had similar visual outcomes, %ECL and rejection rate compared with successful primary DMEK eyes, but high % graft failure after re-DMEK

CCT, central corneal thickness; CDVA, corrected distance visual acuity; DMEK, Descemet membrane EK; EC, endothelial cell; %ECL, endothelial cell loss rate; EK, endothelial keratoplasty; F-U, follow-up time; N/R, not reported; PGF, primary graft failure; re-DMEK, repeat DMEK; Rej, rejection.

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re-DMEK for rejection of the primary graft.[53,82] All studies reported regraft failure rates, ranging from 0% to 21.4% (with follow-up times ranging between 3 and 89 mo). Five studies (n = 110 eyes) reported other complications after re-DMEK,[55,81-83,86] including cataract or IOL opacification (n = 4),[55,81,82,86] IOP spikes or glaucoma progression requiring additional medication or surgery (n = 16),[55,82,83,86] macular edema (n = 3),[55,86] pupillary block (n = 1),[55] and corneal ulcer (n = 1).[82]

Secondary DMEK for Eyes With Previous DSEK Grafts

Six publications reported the outcomes of secondary DMEK for eyes with previous DSEK grafts (n = 79; Table 3).[74,88-92] Early reintervention should be considered because fibrotic processes might be anticipated in this setting.[74] DSEK grafts are carefully mobilized using a reverse Sinskey hook or blunt spatula and then explanted. In this setting, adjacent remnants of host DM have been found to be present at the donor-to-host stromal interface in as many as 50% of eyes and, in most cases, in the visual axis.[89] Meticulous search for adjacent remnants of host DM and tags of stroma should thus be performed[91]; these can be removed using a reverse Sinskey hook or a corneal scraper under air after trypan blue staining.[92] Graft tamponade into the recipient's stroma can be made using air or 20% SF6. Proposed techniques to improve the visibility of the AC include the mechanical removal of the edematous corneal epithelium, application of methylcellulose on the corneal surface during surgery, and optimal illumination.[90]

The optical quality of the transplanted cornea can be fully restored by careful removal of the DSEK graft and implantation of a DMEK graft,[88,90] and therefore, DMEK for eyes with poor visual performance after DSEK has gained increasing interest among corneal surgeons. Mean CDVA improved significantly following secondary EK in all studies (n = 79 eyes) over mean follow-up times ranging from 6 to 18 mo (mean preoperative CDVA ranged from 0.50 to 1.72 logMAR, and mean final CDVA ranged from 0.06 to 0.51 logMAR). Two studies (n = 15) reported that 91.7%–100% of eyes reached CDVA ≥20/40 and CDVA ≥20/25 at 6-mo follow-up[88,89]; in these 2 studies, 33%–42% of eyes reached final CDVA ≥20/20.[88,89] Only 1 study compared outcomes between primary DMEK and secondary DMEK after primary DSEK (n = 8)[74] and reported the inferior outcomes in the latter group. Fibrotic changes in the host cornea due to persistent corneal edema after graft failure and suboptimal status of the DM-stromal interface may account for inferior outcomes.[74]

Three studies (n = 56 eyes) reported the rate of CEC loss, with mean %ECL ranging from 34.7% to 43.7% over 6- to 18-mo follow-up periods.[90-92] This outcome is comparable with reported %ECL following primary DMEK.[8] Four studies (n = 59 eyes) reported rebubbling rates, ranging from 0% to 20%.[88,90-92] Four studies (n = 59 eyes) reported rejection rates in this setting, ranging from 0% to 3.8%[87,90-92]; only 1 study documented cases of immune rejection episode (1 eye), which ended in graft failure.[91] All 6 studies reported graft failure rates, ranging from 0% to 19.2% (mean follow-up times ranging from 6 to 18 mo).[74,88-92]

Secondary DSEK for Eyes With Failed Primary DMEK Grafts

Three studies (n = 39 eyes) have analyzed the outcomes of secondary DSEK in cases of failed primary DMEK (Table 4).[93-95] Two studies (n = 18 eyes) used "conventional" DSEK grafts (one using manual preparation of the graft and another one using DSAEK),[93,94] and 1 study (n = 21 eyes) used UT-DSAEK.[95] This approach may be particularly useful during the learning curve of DMEK surgery,[94,95] as well as in some cases, in which significant corneal edema hinders a good visualization of the AC.[93] In the secondary surgery, the 3.0-mm corneal incision fashioned for the primary DMEK is reopened, the primary graft is stained by injecting trypan blue 0.06% into the AC, and then the failed graft is disinserted from the host using a reverse Price-Sinskey hook and removed from the eye using an intraocular forceps. The host posterior stromal bed should be checked for irregularities under air and the AC thoroughly irrigated to remove all remnant graft tissue.[93] The DSEK graft is then inserted through the corneal incision, unfolded, and positioned onto the recipient posterior stroma; all 3 studies used air filling of the AC, leaving a 50% air-filled AC at the end of the surgery.[93-95]

All 3 studies found an improvement in mean CDVA after secondary EK. After excluding eyes with comorbidities (6 eyes in 2 studies), mean final CDVA improved from 0.69–1.52 to 0.06–0.40 logMAR at 6- to 12-mo follow-up analyses.[93-95] The percentages of eyes reaching CDVA ≥20/40, ≥20/25, and ≥20/20 ranged from 62% to 100%, 0% to 92%, and 0% to 31%, respectively.[93-95] The study of UT-DSAEK for failed DMEK reported better visual outcomes than those of conventional DSEK/DSAEK. In eyes undergoing conventional DSEK/DSAEK for failed DMEK, 62%–87% reached CDVA ≥20/40, and only 1 case in both studies reached CDVA ≥20/25 (range, 0%–13%)[93,94]; in contrast, in the study by Graffi et al,[95] 92% of eyes undergoing UT-DSAEK for failed DMEK reached CDVA ≥20/25, and 30% reached CDVA ≥20/20. These differences likely reflect the influence of graft thickness and regularity of the donor graft on visual performance following DSEK, although the role of the learning curve and experience in DMEK surgery may also play a role in these outcomes because DSEK publications antedated that of UT-DSAEK by 5–8 y. One study found an increase in central corneal light scattering after secondary DSAEK performed after a failed DMEK compared with primary DSAEK eyes.[94]

Two studies (n = 31 eyes) reported CEC loss rates 12 mo after secondary DSEK after failed primary DMEK, ranging between 38% and 46.4%.[93,95] The differences between manually prepared DSEK and UT-DSAEK were not statistically significant (mean difference = 7.2%; $P = 0.531$). Two studies (n = 31 eyes) reported rebubbling rates ranging from 0% to 30%, in favor of UT-DSAEK.[93-95] Only 1 study (n = 21 eyes) reported outcomes regarding allograft rejection episodes after secondary EK in this setting and found no cases of rejection episodes in the first postoperative year.[95] None of the 3 studies reported cases of failed regraft. Only 1 study (n = 21 eyes) reported other complications after secondary EK,[95] with a 23.8% complication rate (graft wrinkling, 1 eye; and IOL opacification in 4 eyes, 2 of which required IOL exchange).[95]

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TABLE 3.

Outcomes of secondary DMEK following primary DSEK

Author	Journal (mo/y)	Eyes (n)	Patient age (y)	Secondary EK	Fuchs indication for primary EK (%)	Ocular comorbidities (%)	Time between primary and secondary EK (mo)	F-U time after secondary EK (mo)	CDVA before secondary EK	Mean preoperative CCT (μm)	CDVA after secondary EK	% Eyes reaching CDVA ≥20/40	%ECL	Mean final CCT (μm)	Rebubbling rate (%)	Rejection rate (%)	Graft failure rate (%)	Comments
Ham et al[88]	*Cornea* (Nov/2010)	3	53.0±10.7	DMEK for poor visual outcome following DSEK	100%	0%	20.0±4.3	6	0.50±0.31 logMAR	620.7±37.5	0.07±0.05 logMAR	100%	N/R	509.7±18.8	0%	0%	0%	Functional results after secondary DMEK for poor visual outcome of primary graft comparable to primary DMEK
Dirisamer et al[89]	*Acta Ophthalmologica* (Mar/2013)	12	66±13	DMEK for poor visual outcome following DSEK	91.7%	25%	32±17	6	0.57±0.38 logMAR	670±112	0.06±0.12 logMAR	91.7%	Final ECD 1709±461 cells/mm^2	517±57	N/R	N/R	0%	Secondary DMEK allows complete visual recovery in eyes with poor visual outcomes after primary DSEK
Brockmann et al[74]	*JAMA Ophthalmol* (Jul/2015)	8	79.4±7.2	DMEK for graft failure following DSEK	N/R	25%	21.4±17.8	12	1.13±0.50 logMAR	900±209	0.38±0.36 logMAR	N/R	Final ECD 908±143 cells/mm^2	524±27	N/R	N/R	0%	Functional results after secondary DMEK for graft failure inferior to primary DMEK
Weller et al[90]	*Am J Ophthalmol* (Jun/2015)	15	67.3±10.2	DMEK for graft failure following DSEK	93%	0%	26±17	18	1.27±0.34 logMAR	917±184	0.14±0.14 logMAR	N/R	43.7% (18-mo F-U)	506±66	13.3%	0%	0%	DMEK showed surgical feasibility in eyes with failed DSEK, with good adhesion of the graft and good optical quality

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TABLE 3. (Continued)

Author	Journal (mo/y)	Eyes (n)	Patient age (y)	Secondary EK	Fuchs indication for primary EK (%)	Ocular comorbidities (%)	Time between primary and secondary EK (mo)	F-U time after secondary EK (mo)	CDVA before secondary EK	Mean preoperative CCT (μm)	CDVA after secondary EK	% Eyes reaching CDVA ≥20/40	%ECL	Mean final CCT (μm)	Rebubbling rate (%)	Rejection rate (%)	Graft failure rate (%)	Comments
Sorkin et al[91]	*Cornea* (Jun/2018)	26	71.9 ± 12.6	DMEK after primary DSAEK (failed graft 70% or suboptimal visual outcome 30%)	57%	50%	8.5 ± 13.0	15.1 ± 10.6	0.84 ± 0.50 logMAR	N/R	0.51 ± 0.49 logMAR	N/R	39.7 ± 22.3% (6-mo F-U)	N/R	11.5%	3.8%	19.2%	Search for remnant islands and tags of stroma in the host interface area should be meticulous after removing the old DSEK graft
Agha et al[92]	*Clin Ophthalmol* (Mar/2019)	15	73.6 ± 7.6	DMEK for graft failure following DSEK	80%	N/R	15 ± 8	12	1.72 ± 0.62 logMAR	869.0 ± 209.9	0.23 ± 0.24 logMAR	N/R	34.7% (12-mo F-U)	511.7 ± 67.7	20%	0%	6.7%	Visual acuity and optical quality were effectively improved even in patients with longstanding corneal decompensation

CCT, central corneal thickness; CDVA, corrected distance visual acuity; DMEK, Descemet membrane endothelial keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty; DSEK, Descemet stripping endothelial keratoplasty; ECD, endothelial cell density; %ECL, endothelial cell loss rate; EK, endothelial keratoplasty; F-U, follow-up time; N/R, not reported.

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TABLE 4.

Secondary DSEK for failed primary DMEK graft

Author	Journal (mo/y)	Eyes (n)	Patient age (y)	Secondary EK	Fuchs indication for primary EK (%)	Ocular comorbidities (%)	Time between primary and secondary EK (mo)	Follow-up time after secondary EK (mo)	CDVA before secondary EK	Mean pre-operative CCT (μm)	CDVA after secondary EK	% Eyes reaching CDVA ≥20/40	%ECL	Mean final CCT (μm)	Rebubbling rate (%)	Rejection rate (%)	Graft failure rate (%)	Comments
Dapena et al[93]	*Br J Ophthalmol* (Feb/2010)	10	67.6 ± 12.0	DSAEK for failed primary DMEK (primary graft failure)	100%	20%	0.8 ± 0.2 (2–5 wk)	12	0.69 ± 0.41 logMAR	N/R	0.40 ± 0.23 logMAR	70% (87% after excluding eyes with comorbidities)	46.4% (12-mo F-U)	N/R	30%	N/R	0%	Secondary DSEK after failed primary DMEK may yield similar clinical outcomes compared with primary DSEK.
Arnalich-Montiel et al[94]	*Graefes Arch Clin Exp Ophthalmol* (Nov/2013)	8	62.1 ± 8.2	DSAEK for failed primary DMEK	100%	0%	1.7 ± 0.8	6	0.65 ± 0.22 logMAR	N/R	0.24 logMAR (range, 0.13–0.52)	62%	N/R	N/R	N/R	N/R	0%	Increased corneal scattering after secondary DSAEK following primary DMEK compared with primary DSAEK eyes, which has a negative impact on visual acuity.
Graffi et al[95]	*Br J Ophthalmol* (May/2018)	21	69.2 ± 7.2	UT-DSAEK for failed primary DMEK	85.7%	19%	3.0 ± 2.1	12	1.52 ± 0.57 logMAR	N/R	0.06 ± 0.05 logMAR (after excluding eyes with comorbidities)	100%	38.9% (12-mo F-U)	N/R	0%	0%	0%	Complication rate 23.8%.

CCT, central corneal thickness; CDVA, corrected distance visual acuity; DMEK, Descemet membrane endothelial keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty; DSEK, Descemet stripping endothelial keratoplasty; %ECL, endothelial cell loss rate; EK, endothelial keratoplasty; F-U, follow-up time; N/R, not reported; UT-DSAEK, ultrathin DSAEK.

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Postoperative Care and Optimization of Graft Survival

As mentioned earlier, EK grafts are considered low risk for immune rejection episodes. Typical postoperative regimens to reduce the risk of allograft rejection episodes after primary EK include topical corticosteroid therapy with tapering over 6–12 mo.[31,38,41] Our immune rejection prophylaxis regimen after EK includes tobramycin 0.3% and dexamethasone 0.1% eye drops every 2 h in the first postoperative day, then 6 times a day for the first postoperative week, then 4 times a day for 4 wk, and then tapering the topical steroids over the following 3 mo, plus dexamethasone 0.05% and chloramphenicol 1% ointment at bedtime for 12 wk, and then at bedtime 3 times weekly until the sixth postoperative month.[19] In addition, we also include oral methylprednisolone 40 mg daily for 3 d, then 20 mg daily from postoperative day 4 to 6, then 10 mg daily during the second postoperative week, and then 10 mg every 48 h during the third postoperative week. We also include topical timolol eye drops twice daily for 3 mo and oral acetazolamide in the first postoperative day to prevent IOP spikes and corticoid-responsive IOP elevations. However, recent evidence suggests that continued use of a topical corticosteroid may be protective against rejection episodes after the first postoperative year following DMEK.[41,96] The reported postoperative rejection prophylaxis protocols after secondary EK are usually the same as for primary EK.[55,82,83] In contrast, repeat PKP is considered a high-risk keratoplasty scenario, and in addition to continuing topical corticosteroids indefinitely, many corneal surgeons also advocate the use of systemic immunosuppressants to reduce the risk of allograft rejection; these include systemic corticosteroids, mycophenolate mofetil, cyclosporine A, rapamycin, and tacrolimus.[46,97] However, the evidence for the effects of immunosuppressants is limited at present.[46,98]

Fourteen studies (n = 275 eyes) reported rejection rates (excluding single-patient case reports). Five eyes had allograft rejection episodes (average rejection rate = 1.8%; range, 0%–50%), which is comparable with the mean 1.9% rejection rate following primary DMEK reported by the American Academy of Ophthalmology.[8] One case of re-DMEK rejection had previous history of immune rejection of the primary DMEK graft,[82] and 1 case of re-DMEK rejection occurred in an eye with previously rejected DMEK graft performed for failed PKP.[55] Three of the 5 regrafts with rejection episodes eventually failed (2 re-DMEK eyes and 1 DMEK for failed primary DSEK graft).[55,91] One retrospective study of repeat DSEK eyes found that these eyes may have a higher risk of allograft rejection compared with primary DSEK (Moura-Coelho et al, personal communication, 2019). These findings raise the question as to whether secondary EK eyes (as well as eyes undergoing EK for failed PKP) graft may be at a higher risk of graft rejection and rejection-related graft failure, compared with the low risk of rejection-related graft failure of primary EK eyes. An aggressive steroid regimen may be needed in the postoperative period, at least in the subset of patients undergoing repeat keratoplasty for graft rejection.[54,78] In these cases, a longer duration or indefinite period of topical corticosteroid prophylaxis could be considered, with careful attention to IOP rises or development or progression of glaucoma.[38] Interestingly, Alió del Barrio et al[84] have suggested adding oral steroids for 1 mo plus topical tacrolimus 0.03% and systemic tacrolimus 1 mg every 12 h in a case of repeat DMEK for primary DMEK failure due to allograft rejection, and the regraft did not experience rejection episodes.

A potential cause of increased %ECL and graft failure after DSEK and DMEK is viral infection caused by herpes simplex virus (HSV) or cytomegalovirus (CMV). When considering retransplantation in a failed corneal graft, the clinician should maintain a high index of suspicion for CMV and HSV infection as potential causes of graft failure.[99] HSV-1 antigen immunoreactivity has been detected in 2%–14% of failed DSEK grafts,[7,100] and HSV endotheliitis should be kept in mind in the early postoperative period after DMEK.[101] CMV endotheliitis after corneal transplantation is an increasingly recognized complication and may be at least as common as graft rejection in Asia,[99] although this has not been confirmed in a study conducted in the United Kingdom.[102] Viral endotheliitis post-EK can closely resemble EK graft rejection with keratic precipitates and mild anterior uveitis, and it is important to differentiate endotheliitis from rejection because the immunosuppressive treatment for rejection episodes can exacerbate the infection. This diagnosis should be suspected in eyes with presumed episodes of allograft rejection unresponsive to steroids, in eyes with hypertensive anterior uveitis, and in eyes with unexplained EC loss in relatively quiet eyes.[103] Viral endotheliitis tends to occur earlier postoperatively usually within the first postoperative year compared with immune rejection episodes.[104] Clinical findings for eyes with AC inflammation after keratoplasty may be indicative of the cause of the inflammation, and IOP elevation may mirror the activity of the endotheliitis in cases of HSV and CMV endotheliitis.[105] A relatively low threshold for aqueous paracentesis and CMV-DNA and HSV-DNA polymerase chain reaction (PCR) analysis have been proposed by some authors,[99] who perform aqueous PCR to exclude viral endotheliitis before treating for immune rejection.[104]

With expanding indications for EK in recent years, there is a growing experience with EK for the indication of corneal decompensation secondary to HSV or CMV endotheliitis. In eyes with HSV-related corneal endothelial failure, DMEK leads to improvement in CDVA, although visual recovery is limited compared with DMEK for other causes.[106] Importantly, these eyes have a higher rate of postoperative complications, including PGF and recurrence of endotheliitis in 12% and 29% of eyes, respectively.[106] One study has found promising outcomes of DMEK in this setting; the disease should be quiescent for ≥6 mo before surgery, that PCR for HSV be performed and be negative 10 d before surgery, and that intensive, perioperative prophylactic oral antiviral and topical antiviral therapy should be continued for at least 1 y to prevent recurrence.[107] Some corneal surgeons suggest keeping topical antivirals indefinitely to reduce the risk of recurrence and subsequent graft failure in eyes undergoing EK for HSV-related endotheliitis.[108]

In the setting of EK for CMV-related corneal endothelial failure, the management of post-EK recurrent endotheliitis is challenging for corneal specialists. In one study, all the patients with detectable CMV-DNA in the aqueous at the time of keratoplasty developed CMV endotheliitis postkeratoplasty and experienced graft failure.[109] Moreover, one

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study found that patients diagnosed with CMV endotheliitis before EK are more likely to have recurrent endotheliitis within the first postkeratoplasty year, even when preoperative anti-CMV treatment and confirmed eradication of CMV and ocular inflammation before keratoplasty were performed.[104] Early recognition and effective treatment are therefore indicated to optimize graft survival following EK in this setting.[110] Optimizing IOP and ensuring quiescence of intraocular inflammation before transplantation is advocated. Preoperative aqueous PCR analysis for CMV-DNA has been recommended before corneal transplantation by some authors.[110] In their center, CMV-positive patients should undergo a systemic and topical antiviral treatment and only after repeat PCR becomes negative in EK performed; postoperatively, the patient is kept on prophylactic systemic oral antiviral therapy for 3 wk and on long-term topical ganciclovir therapy, and a repeat aqueous CMV-DNA PCR analysis is performed to ensure no recurrence of infection.[110] Long-term topical ganciclovir may prevent recurrence of CMV-associated graft failure after EK.[111] Notably, no optimal treatment regime for CMV corneal endotheliitis has been established to date. Intravenous ganciclovir and oral valganciclovir have shown comparable efficacy for CMV disease in solid organ recipients,[112] and this has been extrapolated for keratoplasty by corneal surgeons. Cessation of treatment of CMV endotheliitis has been based on clinical response, with a conservative goal of maintaining 3 mo of antiviral therapy after clinical resolution coupled with a negative aqueous CMV-DNA analysis.[99]

DISCUSSION

Our study provides good evidence that secondary EK renders surgical feasibility and significant improvement in visual acuity and has a good safety profile. Table 5 summarizes the main functional and anatomical outcomes for each scenario in secondary corneal endothelial transplantation. Although both secondary DSEK and secondary DMEK produce significant functional improvement with comparable safety profiles, the findings in this review suggest that eyes undergoing secondary DMEK or secondary UT-DSAEK *may be* more likely to reach higher levels of visual acuity compared with eyes undergoing secondary DSEK (Table 5). However, the quality of this evidence is low, as few publications have reported the proportions of eyes with higher levels of visual acuity. We consider that reporting the proportion of eyes reaching CDVA ≥20/40, ≥20/25, and ≥20/20 should be made a standard of quality in future studies of EK (both primary and subsequent grafts) and that further studies are needed to ascertain whether visual outcomes after secondary DSEK are comparable with those of secondary DMEK.

The visual outcomes following primary and secondary EK in the setting of corneal endothelial failure have been consistently superior to those of repeat PKP. Although repeat PKP produces significant visual improvement, visual outcomes are decreased in eyes undergoing multiple regrafts, with a lower proportion of eyes achieving higher levels of visual acuity.[42,45,46,113,114] Importantly, PKP may also be considered in some cases of failed EK when there is significant opacification of the anterior cornea. Particular considerations in the operative protocol compared with primary EK surgery are to be taken into consideration in secondary EK. Identification and correction of potential factors influencing graft failure (eg, glaucoma, IOL, infection) should be addressed preoperatively and at the time of the surgery.

Our review has several limitations, and it highlights several knowledge gaps that warrant further research efforts concerning secondary EK. First, most available studies to date are retrospective with short follow-up times, and there is a lack of prospective studies. In addition, most studies represent relatively small case series, although this is expected given that DMEK and DSEK are recent techniques. Visual outcomes are likely comparable with those of virgin primary EK eyes, although this is not definite. A shorter interval between graft failure and regrafting likely influences positively the visual outcomes of secondary EK before fibrotic changes induced by corneal edema ensue. Complication rates following secondary EK, including the CEC loss rate, rebubbling rate, and allograft rejection rate, may also be comparable with those of primary EK, and the complication rates following secondary DSEK and secondary DMEK seem to be comparable (Table 5). However, careful preparation and manipulation of the graft is warranted in secondary EK to minimize EC loss. Likewise, meticulous removal of potential graft remnants under air must be performed to optimize the adherence of grafts, particularly in eyes in which GD occurred in the primary graft, as these eyes may be at a higher risk of detached regraft. Immune rejection protocols in secondary EK may require longer-term steroid therapy or even indefinite steroid therapy, particularly in cases of immune rejection of the primary graft.

Finally, secondary EK grafts may be at a higher risk of failure compared with primary grafts, raising the question as to whether these should be regarded as a slightly higher-risk group compared with primary EK eyes. In a large analysis of EK procedures performed in Medicare beneficiaries, 11.6% of eyes underwent repeat keratoplasty, and approximately 17% of eyes received >1 repeat graft.[56] This is in line with the notion that repeat PKP grafts are high-risk corneal transplants, and in these cases, rejection episodes occur in 30%–60% of grafts and up to 70% will fail within 10 y despite local or systemic immunosuppression.[46] It must be emphasized, however, that suboptimal surgical technique in the primary EK procedure may also contribute to increased risk of poor adherence of the secondary EK grafts. Prospective, multicenter, comparative studies are encouraged to determine whether medium- and long-term rates of EC loss and graft failure after secondary EK are comparable with primary EK. In these eyes, promoters of EC proliferation and migration, such as Rho kinase inhibitors, may have a particularly relevant role in improving graft transparency and survival.[46,115,116]

In conclusion, with the growing experience and expanding indications for corneal endothelial transplantation, surgeons dealing with EK surgery will find an increasing number of patients with failing DSEK and DMEK grafts. In these cases, secondary EK grafts provide significant visual improvement. Importantly, our literature review raises relevant questions in secondary EK surgery for which additional studies are strongly encouraged. These include (1) understanding if secondary DMEK or secondary UT-DSAEK are associated with better visual outcomes

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TABLE 5.

Summary of findings regarding outcomes following secondary endothelial keratoplasty

Clinical setting	Studies (eyes, n)	F-U (mo)	CDVA after secondary EK	% Eyes reaching CDVA ≥20/40	% Eyes reaching CDVA ≥20/25	%ECL	Rebubbling rate (%)	Rejection rate (%)	Graft failure rate (%)	Comments
Repeat DSEK/DSAEK[61-70]	10 (403)	6–27	0.50–0.18 logMAR (Snellen 20/30–20/63)	20%–100%[a]	0%[b62]	36.7%–47.3% (6–27 mo F-U)	0%–15%	1 of 54 eyes (1.9%) Range, 0%–50%	0%–20%	Repeat DSEK graft survival may be lower compared with primary grafts,[65] although this is not consensual.[64]
Repeat DMEK[55,80-86]	8 (130)	3.3–14.5	0.33–0.09 logMAR (Snellen 20/25–20/43)	82%–100%	13.3%–81%	34%–49.8% (6–14.5 mo F-U)	5.9%–33%	3 of 104 eyes (2.8%) Range, 0%–14.3%	0%–21.4%	Most, but not all, studies suggest visual outcomes are comparable between primary and secondary DMEK; 18.2%–61% of eyes reached CDVA ≥20/20[55,81,82]; other reported complications: cataract and IOL opacification, IOP spikes or glaucoma progression, macular edema, pupillary block, corneal ulcer.
DMEK after failed DSEK/DSAEK graft[74,88-92]	6 (79)	6–18	0.51–0.06 logMAR (Snellen 20/23–20/65)	91.7%–100% (6-mo F-U)	91.7%–100%[88,89]	34.7–43.7% (6–18 mo F-U)	0%–20%	1 of 59 eyes (1.7%) Range, 0%–3.8%	0%–19.2%	As many as 33%–42% may reach final CDVA ≥20/20.[87,88] Visual outcomes after DMEK for failed DSEK may inferior to those of primary DMEK grafts, although this is not consensual.
DSEK/DSAEK after failed DMEK graft[93,94]	2 (18)	6–12	0.40 – 0.24 logMAR (Snellen 20/35–20/50)	62%–87%	0%–13%	46.4% (12-mo F-U)[93]	30%[93]	N/R	0%	No studies reported other complications.
UT-DSAEK after failed DMEK graft[95]	1 (21)	12	Mean 0.06 ± 0.05 logMAR (Snellen 20/25 ± 20/86)	100%	92%	38.9% (12-mo F-U)	0%	0%	0%	31% of eyes reached CDVA ≥20/20 in this study. Other complications reported: IOL opacification (2 eyes required IOL exchange).

[a]If reports with ≤2 eyes were excluded from the analysis, the proportion of eyes reaching CDVA ≥20/40 after repeat DSEK/DSAEK would be 20%–82%.[60-64,68]

[b]If reports with ≤2 eyes were excluded from the analysis, no eyes undergoing repeat DSEK reached CDVA ≥20/25.[61]

CDVA, corrected distance visual acuity; DMEK, Descemet membrane endothelial keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty; DSEK, Descemet stripping endothelial keratoplasty; %ECL, endothelial cell loss rate; EK, endothelial keratoplasty; F-U, follow-up time; IOL, intraocular lens; IOP, intraocular pressure; N/R, not reported; UT-DSAEK, ultrathin DSAEK.

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compared with the "conventional" DSEK/DSAEK techniques, and in which clinical scenarios, secondary DSEK or PKP should be considered over secondary DMEK; (2) ascertaining whether the visual outcomes of EK regrafts are comparable with those of primary EK eyes; (3) understanding whether secondary EK eyes are in fact a higher-risk subgroup in corneal transplantation compared with primary EK eyes; and (4) ascertaining whether middle- and long-term endothelial cell loss and regraft failure rates are comparable with those of primary EK.

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Publication III

Moura-Coelho, Nuno, João Paulo Cunha, Nicolàs Amich, Oscar Gris, Felicidad Manero, and José L Güell. 2021. "Secondary DMEK after Failed DSEK Graft in Complex Eyes – Retrospective Case Series." *Journal of EuCornea* 10 (1).

Full Length Article

Secondary DMEK after failed DSEK graft in complex eyes – retrospective case series

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Keywords: endothelial keratoplasty, descemet membrane endothelial keratoplasty, dmek, descemet stripping endothelial keratoplasty, dsek, secondary endothelial keratoplasty, complex eyes

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Purpose

Secondary endothelial keratoplasty (EK) represents an increasingly prominent indication for EK. In particular, Descemet membrane endothelial keratoplasty (DMEK) is emerging as a feasible technique in eyes with failed Descemet stripping endothelial keratoplasty (DSEK) grafts. Our aim was to analyse the anatomical and visual outcomes and safety of secondary DMEK in complex eyes with failed DSEK grafts.

Methods

This study was a retrospective case series of complex eyes undergoing secondary DMEK for failed previous DSEK grafts. Four eyes of four patients were analysed, with a mean patient age of 61.8 ± 20.1 years. Best-corrected visual acuity (BCVA, logMAR) before DMEK ranged from 1.30 logMAR to 1.85 logMAR. We analysed the indication of primary and secondary EK, BCVA before and at the final follow-up observation after secondary DMEK (logMAR), corneal thickness, endothelial cell loss rate (%ECL) and complications.

Results

In eyes with functioning DMEK grafts, BCVA improved from 1.60 logMAR (range 1.30-1.60 logMAR) to 0.12 logMAR (range 0.12-0.40 logMAR) at the last postoperative observation (median follow-up time = 33 months (range 18-78 months)). The final corneal thickness in successful grafts was 520.7 ± 40.4 µm. The mean %ECL was 46.6% ± 10.1%. One eye required rebubbling for graft detachment and ended in graft failure requiring tertiary keratoplasty, and no eyes experienced allograft rejection episodes.

Conclusion

Secondary DMEK is surgically feasible and provides visual improvement after a previous failed DSEK, even in complex eyes with severe comorbidities.

INTRODUCTION

Complex eyes, including eyes with phakic intraocular lens (pIOL)-related corneal oedema, pseudophakic or aphakic corneal oedema, aniridic or vitrectomized eyes, and eyes with prior aqueous shunt procedures, pose surgical challenges in the setting of endothelial keratoplasty (EK) (Price, Price, and Trespalacios 2007) and may be at increased risk for EK graft failure due both to increased iatrogenic endothelial cell loss and late endothelial graft failure. Although Descemet stripping endothelial keratoplasty (DSEK) is generally considered more surgically feasible in these cases and although these patients may be at increased risk of complications following Descemet membrane endothelial keratoplasty (DMEK) (Santaella et al. 2020), an increasing number of corneal surgeons have reported good outcomes of DMEK in complex eyes (Price, Price, and Trespalacios 2007; Karadag et al. 2020; Weller, Tourtas, and

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Kruse 2015; Röck et al. 2014; Helaiwa et al. 2018; Yamada et al. 2018; Yoeruek et al. 2015).

Previously failed corneal grafts (including EK and penetrating keratoplasty (PKP)) are becoming an increasing indication for DMEK (Güell et al. 2019; Yoeruek and Bartz-Schmidt 2013; Ćirković et al. 2015; Baydoun et al. 2015; Price et al. 2015; Sorkin et al. 2018; Moura-Coelho et al. 2020). However, the outcome of secondary DMEK after a failed EK graft in complex eyes is lacking in the literature. The aim of this study was to analyse the functional and anatomical outcomes of DMEK for failed DSEK in these cases.

MATERIALS AND METHODS

We performed a retrospective analysis of the outcomes of DMEK after previously failed DSEK grafts in complex eyes. We considered complex eye cases, including eyes with multiple surgeries, highly myopic eyes with very low scleral rigidity (assessed clinically in eyes with large axial length and observed intraoperatively), eyes with pIOL-related endothelial failure, and small and short eyes with shallow anterior chambers. From a single centre, a series of 215 consecutive DMEK surgeries was performed between January 2014 and June 2020 by a single surgeon (J.G.), including surgeries on four complex eyes of four patients who underwent DMEK after failed DSEK graft. All primary EK surgeries were performed in different centres using Descemet's stripping automated endothelial keratoplasty (DSAEK) technique. All patients signed an institutional review board-approved informed consent form. The study was conducted according to the Declaration of Helsinki.

Similar to the process of performing DMEK after PKP, we consider it especially important to centre the donor lenticule on the old "shadow" of the DSEK lenticule. With this in mind, we selected a diameter for the donor either equally sized or, in some cases, 0.5 mm smaller than the recipient "shadow". Thus, performing descemetorhexis was not required, but we routinely explored the recipient's posterior stroma for irregularities and graft remnants by gentle scraping with a spatula. To ensure graft attachment with the aid of a sulphur hexafluoride (SF6) 20% bubble, patients were instructed on different positioning regimens for the first five days after the surgery. The postoperative treatment protocol was performed as previously described (Moura-Coelho et al. 2020).

Eyes were analysed before DMEK and at the last postoperative observation. Best-corrected visual acuity (BCVA, logMAR) was measured using Snellen visual acuity projection charts. The primary outcome was the change in BCVA at the last observation. Secondary outcomes were corneal thickness measured by anterior segment optical coherence tomography (AS-OCT), rebubbling rate, endothelial cell loss rate (%ECL), rejection rate, and graft failure rate. Statistical descriptive analysis was performed using IBM® SPSS Statistics V23.0 software.

RESULTS

Baseline patient data are presented in Table 1. The indication for primary EK was pIOL-related endothelial failure in two patients, Fuchs' dystrophy in one patient, and pseudophakic bullous keratopathy in another patient. Patient 2 underwent two previous DSAEK surgeries, whereas the other patients had only undergone one previous EK surgery. The mean interval between the last DSAEK and DMEK was 14.2 ± 16.4 months. The mean donor age was 74.0 ± 8.9 years, and the mean graft endothelial cell density was 2525 ± 310 cells/mm^2. The mean death-to-use time was 12.3 ± 0.8 days. Patient 4 was an elderly patient and had a short and small eye (axial length 23.00 mm) with a narrow angle. She had undergone DSAEK for pseudophakic bullous keratopathy, required rebubbling for DSAEK graft detachment at postoperative day 5, and evolved to complete graft re-detachment and primary graft failure, for which she underwent DMEK one month after the primary DSAEK. Data on pre-DMEK corneal thickness were available for patients 1, 2 and 4 with a mean pre-DMEK central corneal thickness of 1039.3 ± 64.7 µm.

One eye (25%) required rebubbling for graft detachment after DMEK and ended in primary failure of the DMEK graft. This patient underwent penetrating keratoplasty (due to patient preference to avoid postoperative head positioning), reaching a BCVA of 0.48 logMAR (Snellen equivalent 20/60) at the 4-month follow-up (Figure 1). No other major perioperative complications were observed.

In the three eyes without primary failure of the DMEK graft (Table 2), the median follow-up time after DMEK was 33 months (range 18-78 months). BCVA improved from 1.60 logMAR or 20/796 Snellen equivalent (range 1.30-1.60 logMAR) to 0.12 logMAR or 20/26 Snellen equivalent (range 0.12-0.40 logMAR). At the final observation, corneal clearing was observed in these three cases (Figure 2). In these eyes, the mean corneal thickness at the last observation was 520.7 ± 40.4 µm. The endothelial cell loss rate ranged between 39-61% with a mean rate of 46.6% ± 10.1%. We observed no episodes of allograft rejection or late DMEK graft failure.

DISCUSSION

An increasing number of studies have provided sound evidence that secondary DMEK results in significant visual improvement after previous DSEK/DSAEK failure with a better optical quality compared with secondary DSEK (Brockmann et al. 2015; Weller et al. 2015). However, secondary DSEK may still be considered in this setting, particularly for corneal surgeons inexperienced in DMEK surgery or in occasional patients with significant corneal oedema hindering good visibility of the anterior chamber. We should also not forget that under some circumstances with significant opacifications in the anterior cornea (especially if considered partially or completely irreversible), PKP might be considered after failed EK. Similarly, we believe that patients with suspicion of significant interface problems or recipient's poor stromal densitometry from previous EK surgery (based on clinical findings or AS-OCT scans) may benefit from undergoing PKP from a potential vision standpoint despite the increased risk of postoperative complications (especially considering the settings of complex eyes). The decision-making process in these complex eyes must be

Table 1. Patient baseline data and donor graft data.

		Patient 1	Patient 2	Patient 3	Patient 4
Patient baseline data	Age (years)	74	35	51	87
	Gender	M	F	F	F
	Laterality	OS	OD	OD	OD
	Indication for primary EK	FECD	pIOL-related endothelial failure	pIOL-related endothelial failure	PPBK
	Time between previous DSEK and DMEK (months)	2	18	36	1
	Ocular comorbidities	Anisomyopic amblyopia OS	High myopia, low scleral rigidity, re-DSAEK	PM (Pstaph, DSM, macular hemorrhage)	Short eye and narrow angle
	Lens status	Pseudophakic	Pseudophakic	Pseudophakic	Pseudophakic
	Previous ocular surgeries	Cataract surgery; DSAEK	pIOL explantation; DSAEK; cataract surgery + re-DSAEK	pIOL explantation; staged cataract surgery / DSAEK / rebubbling for DSAEK graft detachment	Cataract surgery; DSAEK
	Previous EK grafts (n)	1	2	1	1
	BCVA (logMAR)	1.30	1.60	1.60	1.85 (CF)
	Corneal thickness / DSAEK graft thickness (µm)	1098 / 165	970 / 279	-	1050 / 300 *
Donor data	Age (years)	83	79	71	63
	Graft ECC (cells/mm^2)	2100	2700	2500	2800
	Death-to-use time (days)	12	13	13	11

OS – left eye; OD – right eye; EK – endothelial keratoplasty; FECD – Fuchs' endothelial corneal dystrophy; pIOL – phakic intraocular lens; PPBK – pseudophakic bullous keratopathy; DSAEK – Descemet stripping automated endothelial keratoplasty; DMEK – Descemet membrane endothelial keratoplasty; PM – pathologic myopia; Pstaph – posterior staphyloma; DSM – dome-shaped macula; BCVA – best-corrected visual acuity; CF – counting fingers; ECC – endothelial cell count.
*Patient 4 presented with complete DSAEK graft detachment; host corneal thickness on anterior segment optical coherence tomography was 850 µm, and the loose lenticule thickness was 300 µm.

guided by surgeon experience, eye status, history of graft detachment, and patient age.

Nevertheless, evidence of the outcomes of secondary EK in complex eyes is limited. Matsumoto et al. reported successful anatomical and functional results following repeat DSAEK in combination with phakic intraocular lens (IOL) explantation and cataract surgery (Matsumoto et al. 2019). Vasquez-Perez et al. described one case of DMEK following multiple failed EK grafts in an aphakic, vitrectomized eye with a glaucoma drainage device (Vasquez-Perez et al. 2019). Parker et al. reported a case of a 99-year-old patient with a history of severe glaucoma, neo-vascular macular degeneration, and ocular cicatricial pemphigoid who underwent DMEK after a previously failed DSAEK graft (Parker et al. 2020). We present a case series of four complex eyes undergoing DMEK for failed DSAEK grafts. Although small, this series represents the largest series in the literature to the best of the authors' knowledge. The main limitations of our study are its retrospective nature, including the lack of structural analysis of the recipient corneal stroma and the lack of data on preoperative central thickness.

In our study, secondary DMEK was technically feasible in complex eyes with failed previous DSAEK grafts. We believe that these cases could be feasibly treated by corneal surgeons with experience in DMEK surgery; however, this may not be the case for surgeons early in the DMEK learning curve. Graft tamponade into the recipient's stroma can be made using air alone; however, we prefer 20% SF6. Proposed techniques to improve the visibility of the AC include the mechanical removal of the oedematous corneal epithelium, application of methylcellulose on the corneal surface during surgery, and optimal illumination; indirect microscope illumination instead of coaxial and/or additional illumination with the endo-ocular lighting probe is a very useful

Table 2. Outcomes of Descemet membrane endothelial keratoplasty (DMEK) after failed Descemet stripping endothelial keratoplasty (DSEK) graft.

	Patient 1	Patient 2	Patient 3	Patient 4
F-U (months)	78	33	18	2
BCVA (logMAR)	0.12	0.12	0.40	1.00
Complications	None	None	None	Re-bubbling; Primary graft failure
ECC (cells/mm^2)	1290	1610	980	N/A
(%ECL)	39%	40%	61%	
Corneal thickness (µm)	535	552	475	N/A

DMEK – Descemet membrane endothelial keratoplasty; F-U – follow-up time; BCVA – best-corrected visual acuity; ECC – endothelial cell count; %ECL – endothelial cell loss rate; N/A – not applicable.

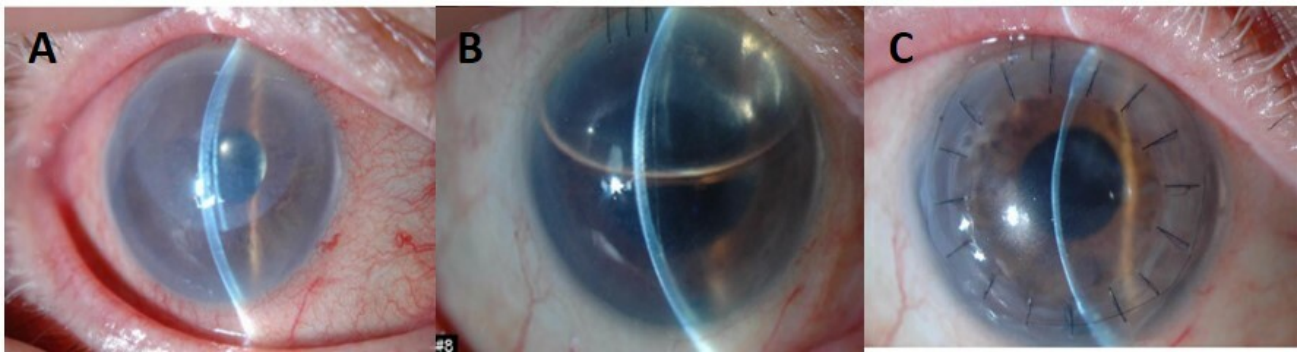


Figure 1. Graft failure following secondary DMEK performed for previous failed DSAEK (figure 1A). Penetrating keratoplasty was performed after DMEK primary graft failure (Figure 1B), with corneal clearing at the 4-month follow-up (Figure 1C).



Figure 2. Anterior segment photographs of the three successful secondary DMEK cases at last follow-up observation (patients 1, 2 and 3, respectively), showing clear corneal grafts.

tool in our experience. Despite a case of graft detachment requiring re-bubbling, we had no cases of apparent graft remnants in this case series, which was consistent with our repeat DMEK surgery experience (Moura-Coelho et al. 2020). Careful removal of the previous graft using a combination of reversed Sinskey and forceps and a meticulous search for remnants under air may minimize the risk of graft remnants in this setting.

In our group of complex eyes, DMEK resulted in visual improvement with visual outcomes comparable to those of previous studies of DMEK after failed DSEK grafts, where the mean final visual acuity ranged from 0.06 to 0.51 logMAR (Moura-Coelho et al. 2021). We also showed that DMEK is effective in improving visual acuity even in eyes with multiple previous DSAEK grafts; similar findings have been observed by Vasquez-Perez et al. (Vasquez-Perez et al. 2019) and in a case of tertiary DMEK we recently reported (Moura-Coelho et al. 2020). Interestingly, however,

these eyes achieved a lower final BCVA compared with our previously reported experience with repeat DMEK (Moura-Coelho et al. 2020), which is likely related to the suboptimal status of the DM-stromal interface that may account for inferior outcomes (Ćirković et al. 2015). Proper densitometry studies will likely aid in understanding the underlying cause of visual loss in these multiple operated eyes (Agha et al. 2019).

We had one case of rebubbling in our cohort that ended in DMEK failure requiring tertiary keratoplasty. Perhaps intraoperative choroidal haemorrhage is the most fearsome complication reported thus far in the setting of complex eyes undergoing DMEK after failed DSEK (Parker et al. 2020), and DMEK in complex eyes may be associated with increased complication rates (Bachmann et al. 2019; Santaella et al. 2020). However, this was not found in the study by Vasquez-Perez et al (2019). DMEK may be preferable to DSAEK in these complex eyes where the risk of transplant rejection is increased (Vasquez-Perez et al. 2019); reported rejection and graft failure rates for DMEK following DSEK range from 0-3.8% and from 0-19.2%, respectively (Moura-Coelho et al. 2021). Of note, our case of DMEK failure due to graft detachment occurred in the setting of a patient with a background of a completely detached DSAEK graft, suggesting that host intrinsic properties may play an important role in graft adhesion and survival (Moura-Coelho et al. 2020).

In conclusion, DMEK for failed previous DSAEK grafts is a feasible procedure with good efficacy and safety profiles even in complex eyes with multiple previous surgeries and comorbidities. With the growing experience and longer track records of DSEK/DSAEK grafts, failure of DSEK grafts will become an increasing indication for DMEK.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts to disclose.

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Publication IV

Clinical Ophthalmology

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ORIGINAL RESEARCH

Descemet's Membrane Endothelial Keratoplasty for Corneal Endothelial Failure Secondary to Three Types of Phakic Intraocular Lens – Retrospective Study

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Purpose: To analyze the outcomes of Descemet's membrane endothelial keratoplasty (DMEK) for corneal endothelial failure secondary to phakic intraocular lens implantation (PIOL) at a reference center for corneal transplantation in Spain.

Design: Retrospective, single-surgeon case series.

Methods: Single-center analysis of patients who underwent DMEK for PIOL-related corneal decompensation between July 2011 and July 2020 with at least 6 months of follow-up postoperatively. Primary outcome was final best-corrected visual acuity (BCVA, logMAR) compared to pre-DMEK BCVA. Secondary outcomes analyzed included post-DMEK refractive spherical equivalent, endothelial cell loss (%ECL), and graft failure.

Results: Sixteen eyes (14 patients) underwent DMEK for PIOL-related corneal decompensation. Mean (SD) time to PIOL explantation was 9.3 (5.0) years, and median (P25-P75) time between PIOL explantation and DMEK surgery was 3 (2–4) months. Median pre-DMEK BCVA was 0.80 (1.08–0.60) logMAR. A statistically significant improvement in BCVA was observed 1 month after DMEK ($p = 0.001$), and median final BCVA was 0.15 (0.0–0.35) logMAR ($p = 0.002$). Mean %ECL was 55.6 (18.7) % at 2-year follow-up and 61.7 (11.7) % in eyes with over 4 years of follow-up. Two eyes required re-bubbling (12.5%), one of which ended in primary graft failure (6.2%) and one eye had late endothelial graft failure (LEGF) at 4-year follow-up (1/15 grafts, 6.7%).

Conclusion: In patients with PIOL-related corneal decompensation, DMEK leads to good and clinically significant refractive and visual outcomes in the medium-long term, with a good safety profile. Prospective studies are encouraged to ascertain whether these cases are at increased risk of accelerated endothelial cell loss and LEGF.

Keywords: descemet membrane endothelial keratoplasty, endothelial keratoplasty, phakic intraocular lens, corneal endothelial failure

Plain Language Summary

- DMEK is safe and effective for corneal decompensation due to phakic IOLs.
- A two-staged approach (phakic IOL explantation, then DMEK) may be preferable.
- DMEK yields good refractive outcomes, relevant in previous refractive surgery cases.
- DMEK in this setting may have an increased endothelial cell loss rate.

Introduction

Despite the excellent long-term efficacy and safety profiles of phakic intraocular lenses (PIOLs) for the correction of moderate-to-high ametropia,[1–4] accelerated endothelial cell loss is still the main concern after PIOL implantation,[4,5]

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being the second most frequent indication for PIOL explantation (after cataract development).[6–10] Up to 3–4% of patients with PIOL-related corneal decompensation may require corneal allograft transplantation. Although endothelial keratoplasty (EK) techniques have demonstrated to be effective for Fuchs' endothelial corneal dystrophy (FECD) and pseudophakic bullous keratopathy (PPBK), there is a paucity of data on the outcomes of Descemet's membrane endothelial keratoplasty (DMEK) and Descemet's stripping endothelial keratoplasty (DSEK) for novel indications, including PIOL-related corneal decompensation.[11–13] Since patients who underwent refractive surgery have higher visual and refractive expectations, endothelial keratoplasty (EK) techniques (particularly DMEK) may offer them better postoperative outcomes compared with penetrating keratoplasty (PKP).

The aim of this study was to analyze the anatomical and functional outcomes of DMEK surgery for PIOL-related corneal decompensation.

Materials and Methods

Study Design and Approval

We conducted a single-center, retrospective, interventional, noncomparative study of all cases of primary DMEK for PIOL-related corneal decompensation. All patients gave informed consent to review their medical records, and patient data confidentiality was guaranteed under the national laws for personal data protection and digital rights guarantee, as well as under the Regulation (EU) 2016/179 of the European Parliament for personal data protection. This study complied with the Declaration of Helsinki and was performed according to ethics committee approval (Comité Ético de Investigación- Instituto de Microcirugía Ocular – CEIm IMO, Spain).

Patients

Between July 2011 and July 2020, sixteen eyes of fourteen patients with PIOL-related corneal decompensation underwent primary DMEK by a single experienced DMEK surgeon (J.L.G.) and had ≥6 months of postoperative follow-up (F-U). All the DMEK cases were performed in our center, but the PIOL patients were from a broad source of referral.

Donor Tissue Protocol

Pre-cut corneal donor tissues for primary DMEK grafts were obtained from the Barcelona Tissue Eye Bank. Corneal tissue donation followed the national regulations for cadaver donors (BOE-A-2012-15715), and this was conducted in accordance with the Declaration of Istanbul. The mean age of the DMEK graft donors was 67.5 (10.7) years, and the mean ECD was 2520.6 (296.1) cells/mm^2.

Surgical Technique

The incisions for DMEK, crystalline lens surgery and "foldable" PIOL explantation were the same, standardly located at 120°. In those cases of PMMA PIOL explantation, an independent incision was created at the surgical limbus and centered at 60°; once it was closed, both crystalline lens surgery and DMEK were performed through a standard 120°-centered 2.4-mm main incision.

All DMEK surgeries were performed under local anesthesia. The surgical technique for primary DMEK surgery was as previously described by our group.[14,15] Briefly, after central descemetorhexis was performed under air and a surgical inferior peripheral iridectomy was made. The donor graft with a diameter 0.5–1.0 mm smaller than the descemetorhexis diameter was gently injected (using the Güell DMEK 2.2 injector, DK220; Medical, Thal, Switzerland), unfolded using indirect corneal manipulation, and 20% sulphur hexafluoride (SF6) was used as ocular endotamponade to ensure graft apposition onto the recipient's posterior stroma. Subconjunctival methylprednisolone was administered at the end of the procedure.

Postoperative Protocol

The postoperative protocol was as our standard, including postoperative positioning regimens to ensure graft attachment,[14] and immune rejection prophylaxis protocol, consisting of a) topical dexamethasone 0.1% every 2 hours

for one day, 6 times daily for one week, then 4 times daily for 4 weeks and then tapered over 3 months and then maintained once daily (with careful monitoring of the intraocular pressure (IOP)); b) dexamethasone 0.05% ointment at night-time for 6 months and then stopped in the absence of inflammatory signs or symptoms; c) oral methylprednisolone slowly tapered off for the first 3 weeks (40 mg/day for 3 days; 20 mg/day for 3 more days; 10 mg/day for 1 week; and 10 mg every 48h for 1 week); and d) topical timolol 0.5% every 12 hours for twelve weeks, with additional IOP-lowering drugs if needed.

Data Collection

We analyzed demographic data (age, gender), time between PIOL implantation and explantation, the BCVA and refractive error (refractive spherical equivalent (RSE), in diopters) before PIOL explantation (± RLE) and before DMEK surgery, and the patients' ECC and corneal pachymetry prior to DMEK. In cases where history was available, we also collected the data regarding the patient's status prior to PIOL implantation surgery, including history of amblyopia or pathologic myopia, pre-PIOL BCVA, pre-PIOL RSE, PIOL type and spherical power.

We analyzed the post-DMEK BCVA at months 1 (M1), 3 (M3), 6 (M6), and at the last F-U observation; in cases with ≥1 or ≥2 years of F-U, these time-points were also analyzed.

Main Outcome Measures

The main outcome was improvement in BCVA at the last F-U observation compared with BCVA before DMEK (baseline).

Secondary Outcomes

Other outcomes analyzed were a) the proportion (%) of eyes reaching final BCVA ≤ 0.30 logMAR (≥20/40 Snellen), BCVA ≤ 0.10 logMAR (≥20/25 Snellen) and BCVA ≤ 0.00 logMAR (≥20/20 Snellen); b) change in RSE at final observation compared with pre-DMEK RSE; c) endothelial cell loss (%ECL); d) re-bubbling rate; e) immune rejection rate; f) primary and secondary graft failure rates; g) change in corneal pachymetry at last F-U compared with pre-DMEK; and h) postoperative complications after DMEK, including IOP spikes, ocular hypertension (OHT) or glaucoma, IOL opacification or cataractogenesis, and cystoid macular oedema (CMO).

Statistical Analysis

SPSS software (v 23.0; IBM Corp, Chicago, Illinois, USA) was used for the statistical analysis. Quantitative variables were described as mean (standard deviation) if they had a normal distribution, and parametric tests were applied in such case; quantitative variables without a normal distribution were described as median (P25-P75), and nonparametric tests were applied. Categorical variables were described in absolute and relative frequencies, and chi-square or Fisher exact tests were applied for comparison between categorical variables. The significance level α was 0.05.

Results

Baseline Data

Table 1 depicts the demographic and baseline data. Mean patient age was 49.2 (14.3) years. Four eyes (25%) had amblyopia, and three eyes (18.8%) had pathological myopia at the time of PIOL implantation. Five eyes (31.3%) had angle-supported PIOLs (AS-PIOL) implanted (Figure 1), two eyes (12.5%) had posterior-chamber collamer PIOLs (PC-PIOL), and the remaining nine eyes (56.2%) had anterior chamber (AC), iris-claw PIOLs (IC-PIOL); mean PIOL spherical power was- 10.20 ± 12.28 D. Two eyes (one patient) had an AC IC-PIOL implanted elsewhere (Worst phakic IOL) and was referred to us for corneal decompensation fourteen years after phakic IOL implantation. Visual acuity data prior to PIOL implantation were only available in four eyes, with a mean BCVA of 0.41 ± 0.28 logMAR. Mean time to PIOL explantation was 9.3 ± 5.0 years, with a mean BCVA prior to PIOL explantation of 0.45 ± 0.35 logMAR. The median time between PIOL (± RLE) and primary DMEK was 3 (2–4) months (range 1–28 months); staged DMEK

Table 1 Patients' Demographics, Preoperative Characteristics, and Cornea Donor Data

Patients' Characteristics	**N = 16 Eyes (14 Patients)**	
Age, years	49.2 (14.3)	
Female gender, n (%)	10 (62.5%)	
Right eyes, n (%)	11 (68%)	
Type of PIOL		
Angle-supported AC-PIOL *Iris-claw AC-PIOL* *PC-PIOL (ICL)*	5 (31.3%) 9 (56.2%) 2 (12.5%)	2 Baikoff, 2 Nuvita, 1 AcrySof Cachet 3 Worst, 4 Artisan, 2 Artiflex
PIOL spherical power, D	− 10.20 (12.28)	
Ocular comorbidities, n (%)	4 (25%) amblyopia, 3 (18.8%) PM	
BCVA before PIOL implantation, logMAR	0.41 (0.28)	
Time between PIOL implantation and explantation, years	9.3 (5.0)	
BCVA prior to PIOL explantation, logMAR	0.45 (0.35)	
Donor characteristics		
Age, years	67.5 (10.7)	
ECC, cells/mm^2	2520.6 (296.1)	
PT, days	5.6 (1.0)	
Baseline (pre-DMEK) data		
Lens status at the time of DMEK surgery, n (%)	1 phakic eye (6.2%), 15 pseudophakic (93.8%)	
Time between PIOL explantation and DMEK, months	3 (2–4)	
Staged DMEK, n (%)	12 (75%)	
Pre-DMEK BCVA, logMAR	0.80 (1.08–0.60)	
Pre-DMEK RSE, D	− 0.88 (−2.56–0.06) D	
F-U, months	37.3 (29.6)	

Notes: Quantitative variables are presented as mean (SD) or as median (P25-P75). Categorical variables are presented as absolute and relative frequencies (n, %).
Abbreviations: DMEK, Descemet's membrane endothelial keratoplasty; PIOL, phakic intraocular lens; AC-PIOL, anterior-chamber phakic intraocular lens; PC-PIOL, posterior-chamber phakic intraocular lens; PM, pathological myopia; BCVA, best-corrected visual acuity; ECC, endothelial cell count; PT, preservation time; D, diopters; F-U, follow-up time following DMEK (months).

(DMEK performed within 4 months of the PIOL explantation) was performed in twelve eyes (75%). Median BCVA prior to DMEK surgery (baseline BCVA) was 0.80 (1.08–0.60) logMAR, with a median RSE of −0.88 (−2.56 – +0.06) D.

Twelve eyes (75%) underwent staged DMEK (DMEK performed within ≤4 months of the PIOL explantation ± refractive lens exchange (RLE), and the median time between PIOL (± RLE) and primary DMEK was 3 (2–4) months (range 1–28 months). Fifteen eyes (93.8%) underwent RLE at the time of PIOL explantation. In all cases where RLE was performed, presence of posterior vitreous detachment and absence of peripheral retinal lesions that required prophylactic treatment was confirmed before the RLE surgery; one eye (6.2%) remained phakic at the time of the DMEK surgery because PVD was not present. When RLE was performed, IOL determination was based on optical biometry using the IOL Master 500 (until 2016) or the IOL Master 700 (since 2016), and the Haigis formula was adopted in most cases, targeting a residual spherical error between −0.75 and −1.25D.[16]

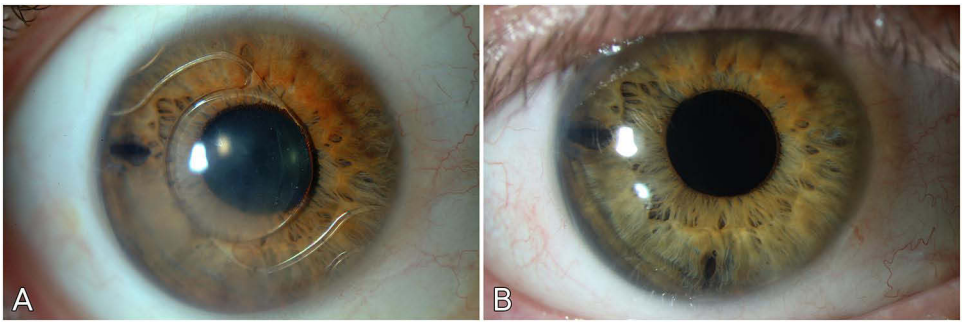


Figure 1 Anterior segment photograph of a patient who underwent DMEK for PIOL-related corneal decompensation. (**A**) Corneal decompensation in an eye with an angle-support, phakic intraocular lens (BCVA = 20/40 Snellen). (**B**) 8 years after staged surgery (PIOL explantation plus RLE, followed by DMEK), showing a clear cornea (BCVA = 20/20 Snellen).

Primary Outcome - Visual Acuity

One eye (6.2%) had primary graft failure following DMEK (PGF) and was excluded from the BCVA analysis. In eyes without PGF (n = 15), mean F-U time was 37.3 ± 29.6 months (range 6–96 months); three eyes (20%) had <12-month postoperative F-U. As a group, median BCVA at last F-U observation was 0.15 (0.00–0.35) logMAR (20/23 Snellen equivalent), which was statistically significantly better compared with baseline BCVA (p-value = 0.002), as well as compared with BCVA before PIOL explantation (p = 0.004). In eyes without ocular comorbidities limiting visual potential, median final BCVA was 0.10 (0.00–0.23) logMAR (p = 0.017).

A statistically significant improvement in BCVA from baseline was observed as early as in the first postoperative month (median BCVA at M1 = 0.42 (0.50–0.20) logMAR; p = 0.001) and again at M3 post-DMEK (median BCVA at M3 = 0.25 (0.30–0.10 logMAR); p = 0.039) and remained stable for the two first postoperative years (Figure 2). Nine eyes (n = 9) had >2-year follow-up after DMEK, the final median BCVA was 0.10 (0.15–0.00) logMAR at 52.9 (28.3) months (not displayed in Figure 2). Three eyes (n = 3) had more than 5 years of F-U, with a final BCVA of 0.25 logMAR (20/25 Snellen) in one eye and 0 logMAR (20/20 Snellen) in the other two eyes.

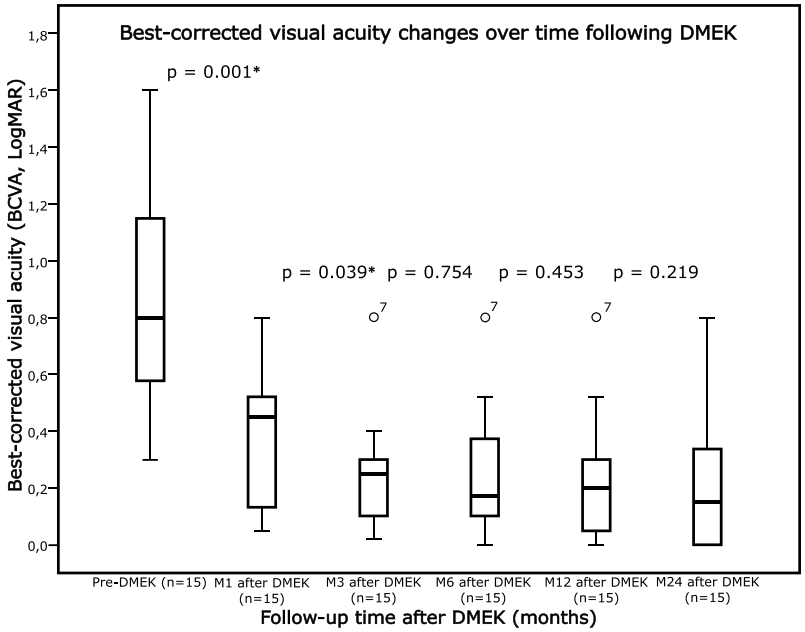


Figure 2 Box-plot charts showing the evolution in BCVA following Descemet's membrane endothelial keratoplasty over a 24-month follow-up period. Statistically significant improvements in mean/median BCVA were observed at postoperative M1 (p = 0.001) compared with baseline pre-DMEK, and again at M3 compared with M1 (p = 0.039). Median BCVA remained stable thereafter during the 2-year follow-up. *P-value < 0.05.

The proportion of eyes reaching final BCVA ≤ 0.30 logMAR (≥20/40 Snellen), BCVA ≤ 0.10 logMAR (≥20/25 Snellen) and ≤0.00 logMAR (≥20/20 Snellen) were 73.3%, 40%, and 26.7%, respectively; after excluding eyes with ocular comorbidities limiting visual potential, these proportions increased to 87.5%, 62.5%, and 37.5%, respectively.

The median final RSE after DMEK was −0.50 (−1.25–0.00) D. One eye remained phakic after DMEK and had a final refraction of −14.25 DS −1.50 DC (160°), and one eye underwent photorefractive keratectomy (PRK) 2 years after DMEK and reached plano refraction.[17] Excluding these two cases, 8 eyes (62%) had a final RSE within ± 0.50 D of emmetropia, and 10 eyes (77%) had a final RSE within ± 1.00 D of emmetropia.

Endothelial Cell Count and Corneal Thickness

Corneal thickness after DMEK decreased from 651.1 ± 66.0 µm to 492.1 ± 37.0 µm. Mean ECC at 2-year F-U was 1042.6 ± 418.0 cells/mm^2), with a mean %ECL of 55.6 ± 18.7%. In eyes with >2 years of follow-up (n = 9), after excluding one eye which had late endothelial graft failure (LEGF) at 4-year follow-up, mean total %ECL was 61.7 ± 11.7% (range = 47–77%). Two eyes (n = 2) had 8 years of follow-up, with a mean %ECL of 69.8 ± 1.2% (Table 2).

Postoperative Complications

Two eyes (12.5%) developed graft detachment requiring re-bubbling, one of which ended in PGF. We observed no cases of immune rejection episodes.

One eye (6.2%) developed CMO 3 months after DMEK, with a BCVA of 0.40 logMAR (20/50 Snellen equivalent), which was resolved at 6-month F-U with intravitreal sustained-released dexamethasone implant injection, maintaining a BCVA of 0.00 logMAR (20/20 Snellen) at 4-year follow-up. Seven pseudophakic patients developed posterior capsular opacification (PCO) during the follow-up. In three eyes, visual acuity at M6 follow-up was hindered by PCO, and these cases had significant improvement in vision following Nd:YAG laser posterior capsulotomy.

DMEK Survival and Graft Failure

In one eye, the cornea (1/16 eyes, 6.2%) failed to clear following DMEK (PGF). This eye had a graft detachment for which rebubbling was performed, although anatomical reattachment was successful, the graft failed and a repeat DMEK was performed.

Table 2 Efficacy and Safety of Descemet Membrane Endothelial Keratoplasty for Phakic Intraocular Lens-Related Corneal Decompensation

	Pre-DMEK	**Post-DMEK**
BCVA (logMAR) RSE (D)	0.80 (1.08–0.60) logMAR − 0.88 (−2.56–0.06) D	0.15 (0–0.35) logMAR −0.50 (−1.25–0) D
ECL (%)	Donor graft ECD = 2520.6 (296.1) cells/mm^2	2-year: 55.6 (18.7)% 4-year (n=9): 61.7 (11.7)% 8-year (n=2): 69.8 (1.2)%
CCT (µm)	651.1 (66.0) µm	492.1 (37.0) µm
Re-bubbling rate (n, %)	–	2, 12.5% (one ending in PGF)
Rejection episodes (n, %)	–	0, 0%
Graft failure (n, %)	–	1 eye PGF (1/16, 6.2%) 1 eye LEGF at 4-year F-U (1/15, 6.7%)
Other complications (n, %)	–	0 intraoperative complications (0%) 1 (6.2%) cystoid macular oedema (resolved with sustained-release 0.7-mg dexamethasone implant [Ozurdex])

Notes: Quantitative variables are presented as mean (SD) or as median (P25-P75). Categorical variables are presented as absolute and relative frequencies (n, %).
Abbreviations: DMEK, Descemet membrane endothelial keratoplasty; BCVA, best-corrected visual acuity; RSE, refractive spherical equivalent; D, diopters; ECL, endothelial cell loss; ECD, endothelial cell density; CCT, central corneal thickness; PGF, primary graft failure; LEGF, late endothelial graft failure; F-U, follow-up.

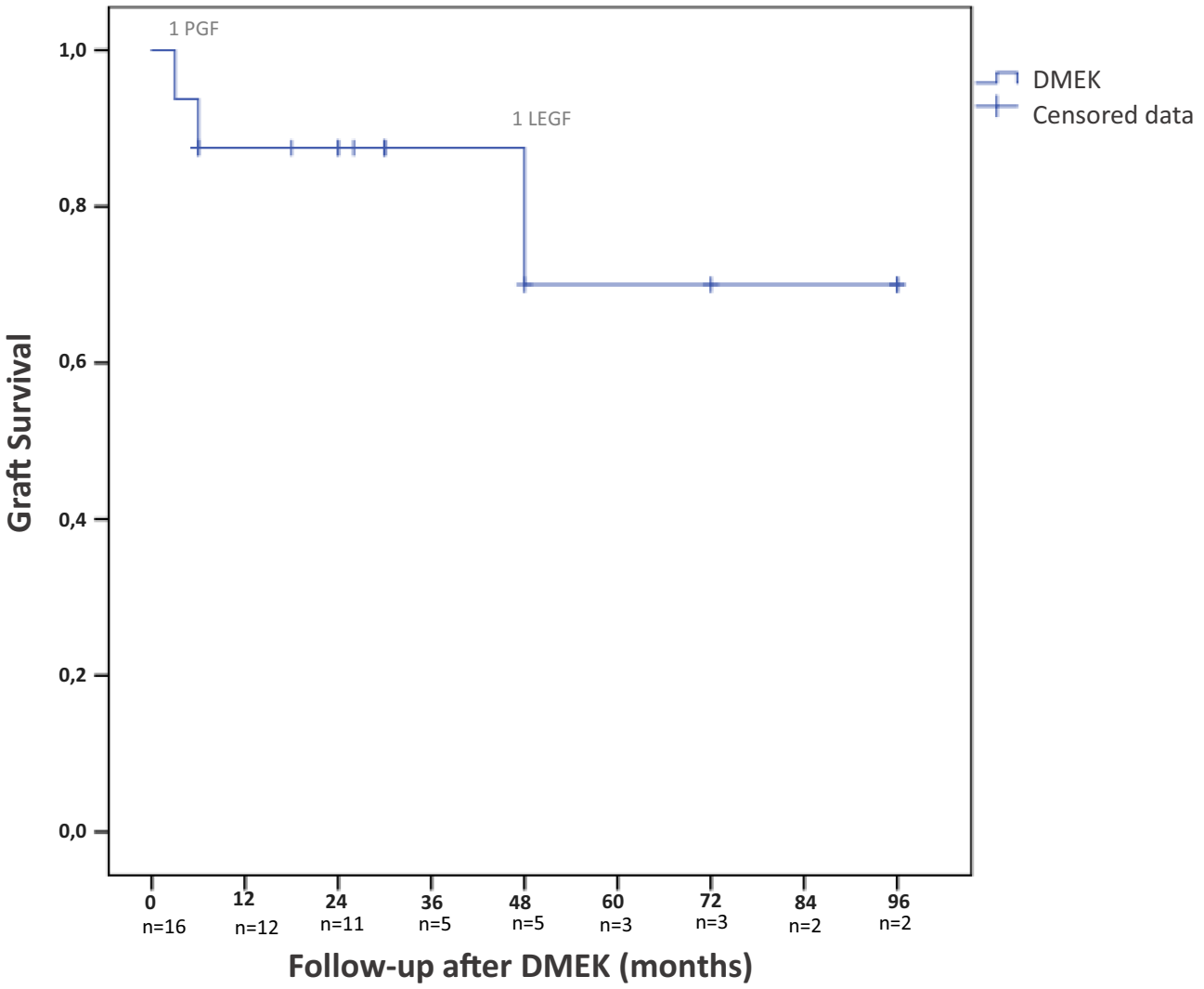


Figure 3 Survival rates after Descemet's membrane endothelial keratoplasty (DMEK) performed for phakic intraocular lens-related corneal decompensation.
Abbreviations: PGF, primary graft failure; LEGF, late endothelial graft failure.

Of the functioning grafts (n = 15), one eye (1/15 eyes, 6.7%) evolved to LEGF (final ECC = 551 cells/mm^2, representing a 73.8% endothelial cell loss), diagnosed at 4-year F-U. This eye also developed OHT following DMEK, which may have been an important contributing factor to increased %ECL and to graft failure. Graft survival rates at 1-year and at 2-year follow-up after DMEK were 93.8%. Five eyes had F-U ≥4 years, with 4 out of those 5 eyes (80%) having clear corneas at 4-year follow-up. Survival rates throughout the follow-up are shown in Figure 3.

Discussion

Although there is an increase in the endothelial cell (EC) loss rate after PIOL implantation,[3,5] the published rates of PIOL explantation due to accelerated EC loss and corneal decompensation are highly variable, ranging from 0% to 32%.[6–9] Phakic IOL explantation for this indication usually occurs over the long term, with reported average times to explantation ranging between 7 and 13.8 years after implantation.[6–9] Although we did not observe cases of intraoperative complications during phakic IOL explantation, this surgery is not without risks and may be technically challenging, and especially in the case of angle supported PIOLs (but also in the cases of iris claw-PIOLs and, to a lesser degree, with PC-PIOLs),

the risk of intraoperative hemorrhage and iris damage is not negligible and may even adversely affect the outcomes of subsequent DMEK surgery.

In our study, DMEK proved feasible in the setting of PIOL-related corneal decompensation, in line with previous reports.[11,12] Although some authors have advocated simultaneous PIOL explantation and EK,[13] we consider that a staged approach is preferable in this setting for two main reasons: 1) the risk of intraoperative bleeding during explantation which would complicate DMEK surgery; and 2) in less severe cases we believe that if the PIOL explantation (± RLE) procedure is uneventful, some patients may retain sufficiently acceptable BCVA to delay or prevent DMEK surgery. In the study of López et al,[12] only one case underwent quadruple procedure (simultaneous PIOL explantation + cataract surgery + DMEK), and it ended in PGF, which supports our notion that a two-staged approach may be preferable. Highly myopic eyes with very deep AC may pose surgical challenges for DMEK surgery. However, collapsing the AC in these myopic eyes can be relatively simple (unlike the challenges with deep AC of aphakic eyes or vitrectomized eyes) by carefully removing small volumes of aqueous humor from the AC via the main incision, and thus unscrolling the DMEK graft in these eyes is feasible by DMEK surgeons who have completed the learning curve of DMEK surgery.

In our study, clinical and statistically significant changes in BCVA occurred as early as 1 month following DMEK, and stability was observed in the medium term. Our findings are similar to those of Fernandez López et al and Liarakos et al.[11,12] Importantly, we also found that BCVA did not significantly deteriorate after multiple surgeries, which is a possible risk owing to factors such as limbal stem cell deficiency, low-grade chronic inflammation, and postoperative complications such as OHT, glaucoma or posterior segment complications. Of note, if eyes with ocular comorbidities limiting visual potential were excluded, we found a high proportion of eyes reaching higher levels of BCVA (≥20/25 and ≥20/20 Snellen), comparable with previous reports of DMEK for other indications.[18–22] Although eyes with PIOL-related corneal decompensation are often considered complicated eyes for DMEK grafting, we have found that DMEK is feasible and resulted in superior visual outcomes compared with DSEK for this indication.[11,23,24]

We have achieved a high proportion of eyes with good refractive outcomes (RSE within 0.50 and within 1.00 D of target refraction). In the setting of PIOL-related corneal decompensation requiring DMEK, the decision to perform RLE is not always straightforward: 1) these patients are usually relatively younger than those undergoing DMEK for other indications, 2) the risk of long-term complications following crystalline lens surgery may be increased, as these eyes are usually highly myopic, 3) corneal transparency may pose a surgical challenge for crystalline lens removal, and 4) IOL power determination may be challenging due the corneal decompensation. However, myopic patients tend to have cataract onset at an earlier age. Besides, cataractogenesis or cataract progression is to be expected following DMEK, and later cataract surgery may put DMEK grafts at risk of EC loss and graft failure. In addition, if RLE is not performed, these patients may be at risk of significant anisometropia and aniseikonia if the fellow eye is left with a PIOL. Finally, these are patients who underwent refractive surgery and who have a higher expectation of spectacle independence. Importantly, in patients in which RLE is considered, the refractive target should be shifted by −0.75 to −1.25 D to compensate the expected hyperopic shift induced by corneal deturgescence.[16,25,26]

We observed a mean %ECL of 55% at 2 years, and of 61% in eyes with medium-long term follow-up times (range 2.5–8 years). Our EC loss rates were considerably lower than those of a previous study.[12] However, our 2-year EC loss was somewhat higher than the reported average of 48%±16% (although within this range) of a recently published model of EC loss following DMEK.[27] Besides, these rates appear to be higher compared with our own results for DMEK for other indications,[15,19] as well as with medium-term DMEK studies, where reported %ECL 4 to 5 years after DMEK ranged between 48% and 59%.[20–22,28] Finally, in the two eyes with 8-year follow-up, we observed an average EC loss rate comparable to that reported 10 years after DMEK.[22] Taken altogether, these findings suggest that these eyes may be at risk of accelerated EC loss following DMEK. This has also been reported in one study which reported a 42–47% EC loss rate at 6-month follow-up,[11] and in another study where the authors observed an average of 77% EC loss one year after DMEK.[12] Potential factors contributing to increased EC loss in this setting may include iris changes and chronic low-grade subclinical AC inflammation. We additionally postulate that the presence of PIOL induces a significant EC loss also at the periphery of the corneal endothelial layer, which probably relates with the observation of higher EC loss; this may be the case especially in angle-supported PIOLs, or possibly with PC-PIOL with a narrow angle or a large vault. Increased EC loss may pose these eyes at increased risk of LEGF over the medium-to-long term. We have found an 80%

graft survival rate in eyes with ≥4-year follow-up (4 out of 5 eyes with 48-month follow-up), which is lower in comparison with reported 83–96% graft survival rates at 5–7 years for other indications.[20–22,28]

Although this study has a relatively small cohort size, this is the largest study reporting outcomes of DMEK for PIOL-related corneal decompensation to date, with a mean 3-year follow-up period which allows us to draw important conclusions regarding visual outcomes and complications after DMEK. In addition, it provides relevant insight into the refractive aspects of DMEK surgery, reinforcing the notion that DMEK may be ideal in managing corneal decompensation in refractive patients.[29] Although in our study one eye underwent PRK after DMEK with excellent outcomes, keratorefractive surgery in DMEK eyes must be decided with great caution, since corneal deturgence after DMEK may be associated with a thinner-than-normal central cornea, steeper pachymetric progression from the thinnest point to the periphery, and higher posterior elevation values.[17]

In conclusion, DMEK is surgically feasible in eyes with PIOL-associated corneal decompensation, resulting in early, clinically significant visual improvement, and with a high proportion of eyes reaching high levels of BCVA and very good refractive outcomes. However, these eyes may have an increased rate of EC loss following DMEK and thus a higher risk of LEGF. We consider that larger, prospective studies are needed to ascertain two main aspects: 1) whether PIOL-related corneal decompensation is associated with inferior outcomes compared with DMEK performed for other indications such as Fuchs' dystrophy and 2) to determine whether a two-staged approach has a superior efficacy and safety profile compared with simultaneous PIOL-explantation and crystalline lens surgery.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Dr. Güell has been a consultant for Alcon, Ophtec, Meditec Zeiss, Kowa Co Ltd, Théa Laboratories, RxSight, and Calhoun Vision. Dr. Moura-Coelho, Dr. Cunha, Dr. Dias-Santos, Dr. Dutra-Medeiros, Dr. Papa-Vettorazzi, and Dr. Manero have no conflicts of interest in this work.

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Outcomes of cystoid macular edema following Descemet's membrane endothelial keratoplasty in a referral center for keratoplasty in Spain: retrospective study

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The aim of this study was to analyze the outcomes of eyes with visually significant cystoid macular œdema (vs-CMO) after Descemet membrane endothelial keratoplasty (DMEK) in a referral center for keratoplasty in Spain. We conducted a retrospective, single-surgeon case series of eyes that developed post-DMEK vs-CMO performed between January 2011 and December 2020. Data collected included: indication for DMEK; biometric data; ocular comorbidities; past medical history; time to detection of vs-CMO after DMEK (T, weeks); best-corrected visual acuity (BCVA, logMAR) and central retinal thickness (CRT, µm) at diagnosis of vs-CMO, after resolution of CMO, and at last follow-up; and management strategy. Main outcomes analyzed were incidence of vs-CMO, improvement in BCVA and CRT after treatment of vs-CMO. Of 291 consecutive DMEK surgeries, 14 eyes of 13 patients (4.8%) developed vs-CMO. Five patients (38.5%) had history of CMO, and 28.6% of eyes had ophthalmic comorbidities. Median (P25-P75) T was 4 (3–10) weeks. Treatment success was observed in 12/13 eyes (92.3%), two of which required second-line treatment. In successful cases (median time-to-resolution 3.0 (2.0–3.5) months), median BCVA improved from 0.60 (0.40–0.80) logMAR to 0.30 (0.15–0.40) logMAR (p = 0.002) after treatment, and median CRT improved from 582.5 (400.0–655.0) µm to 278.0 (258.0–294.0) µm (p = 0.005). In our study, we found a 4.8% rate of post-DMEK vs-CMO, with most cases occurring in the first 3 months after surgery. Good functional and anatomical outcomes are expected in most eyes, without treatment-related complications or implications in graft outcomes. Additional studies are encouraged to determine a standardized protocol for post-DMEK vs-CMO.

Endothelial keratoplasty (EK) techniques have become the gold standard for the treatment of corneal endothelial failure, given the better visual outcomes, faster visual recovery, more predictable refractive error and astigmatism, and lower complication rates compared with penetrating keratoplasty (PKP)[1].

Postoperative cystoid macular oedema (CMO) is the most frequent posterior segment complication reported after EK[2,3], including both Descemet stripping endothelial keratoplasty (DSEK) and Descemet membrane endothelial keratoplasty (DMEK), but even so the incidence of CMO after EK compares favourably with its incidence after PKP[4].

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Importantly, most studies of CMO after DMEK have focused on detection of CMO at postoperative spectral-domain optical coherence tomography scans (SD-OCT), but to the best of the authors' knowledge few studies have focused on the outcomes of "visually significant cystoid macular oedema" (vs-CMO)[4–7]. Treatment of post-DMEK CMO is usually favourable, but different first-line treatments have been proposed and few reports are available[3,5,8,9].

The aim of this study was to assess the proportion of eyes that developed vs-CMO following DMEK, and to analyse the anatomical and visual outcomes of post-DMEK vs-CMO in a referral centre for DMEK in Spain.

Materials and methods

Study design and approval. This was a retrospective, observational case series of eyes that developed vs-CMO after DMEK. All patients signed an institutional review board-approved informed consent. The study was conducted according to the tenets of the Declaration of Helsinki.

Visually significant CMO after DMEK was defined as:

- The presence of intra- or sub-retinal fluid in the foveal region detected by macular SD-OCT scans in patients where CMO was suspected;
- Cystoid macular edema was suspected on the basis of a lower-than-expected postoperative visual acuity: despite a clear cornea after DMEK and/or the absence of abnormal de novo funduscopic findings"[5,6].

Surgical technique and postoperative protocol. Pre-cut corneal donor tissues for primary DMEK grafts were obtained from the Barcelona Tissue Eye Bank. DMEK surgeries were all performed by a single surgeon (J.G.).The surgical technique for primary DMEK surgery was as previously described by our group[10,11]. DMEK graft positioning onto the recipient posterior stroma was performed using 20% sulfur hexafluoride (SF6) as tamponade. Subconjunctival dexamethasone 80 mg was administered at the end of the surgery. To ensure graft attachment with the aid of SF 20% bubble, patients were instructed on different positioning regimens in the early postoperative period, as we have previously described[10,11].

Postoperative treatment was as we previously described[12,13], and consisted of topical tobramycin 0.3% and dexamethasone 0.1% (Tobradex; Alcon Cusi, El Mas Nou, Barcelona, Spain) every 2 h for the first postoperative day, then 6 times daily for one week, then 4 times daily for 4 weeks and then tapering over the following 3 months (reduction in 1 drop every 4 weeks); timolol 0.5% (Cusimolol; Alcon Cusi) eye drops 2 times daily for 12 weeks, with additional ocular hypotensive medications if needed; and dexamethasone 0.05% and chloramphenicol 1% ointment at nighttime (DeIcol; Alcon Cusi) for 6 months. Oral methylprednisolone (Urbason; Sanofi Aventis Pharma SA, Barcelona, Spain) was also prescribed and slowly tapered off for the first 3 weeks: 40 mg/day for 3 days; 20 mg/day for 3 more days; 10 mg/day for 1 week; and 10 mg every 48 h for 1 week. A topical corticosteroid was kept at least once daily indefinitely after DMEK, unless contraindicated in light of significant increases in intraocular pressure.

In patients with vs-CMO after DMEK, first-line treatment consisted of adding a topical non-steroidal anti-inflammatory (NSAID) drug twice daily (either bromfenac 0.9 mg/mL (Yellox, Bausch & Lomb) or nepafenac 0.1 mg/mL (Nevanac, Novartis)) to the topical steroid regime plus oral acetazolamide 250 mg three times per day (plus oral potassium supplementation) until resolution of CMO. In cases of incomplete response to first-line treatment, the second-line treatment consisted of intravitreal injection of corticosteroids.

Data collection. We analyzed the patients' electronic medical records (EMRs) to identify cases where a diagnosis of vs-CMO after DMEK was made. The following data was collected retrospectively from the patients' EMRs: demographic data (age, gender, laterality); indication for DMEK surgery; relevant past medical and ocular history (based on evidence from studies of pseudophakic CMO[14–16] and from previous studies on risk factors for postoperative CMO after DSAEK[17,18]), including diabetes mellitus, glaucoma, retinal disease, uveitis, history of CMO in either the interest eye or in the fellow eye; surgical procedure (whether standalone DMEK or DMEK combined with other intraocular procedures); re-bubbling for partial or complete graft detachment; interval between DMEK and detection of vs-CMO (T, weeks); best-corrected visual acuity (BCVA, logMAR) before DMEK, at time of detection of vs-CMO, at resolution of vs-CMO, and at final follow-up observation (F-U); response to first-line treatments and subsequent treatments performed for vs-CMO; resolution of vs-CMO and time to resolution (months); central retinal thickness (CRT, μm) as measured by SD-OCT in the central ETDRS circle at detection of vs-CMO and at last F-U; other postoperative complications, including intraocular pressure (IOP) spikes, ocular hypertension or glaucoma, IOL opacification or cataractogenesis, immune rejection episodes, and graft failure.

Primary outcomes analyzed included the proportion of eyes (%) developing vs-CMO during the first 6 months after DMEK, % eyes with resolved CMO, and change in BCVA after resolution of vs-CMO compared with BCVA before treatment for vs-CMO. Other outcomes analyzed were improvement in CRT after treatment for vs-CMO; % eyes reaching final BCVA ≤ 0.30 logMAR (≥ 20/40 Snellen), % eyes reaching final BCVA ≤ 0.10 logMAR (≥ 20/25 Snellen) and % eyes reaching final BCVA ≤ 0 logMAR (≥ 20/20 Snellen) at last F-U; and success rate of treatment.

Statistical analysis. Data was collected from the patients' EMRs to a database in Microsoft Excel®, and data was then exported to SPSS software (v 27.0; IBM Corp, Chicago, Illinois, USA) for statistical analysis. Quantitative variables were described as mean (standard deviation) if they had a normal distribution, and

parametric tests were applied in this case; otherwise, variables without a normal distribution were reported as median (P25-P75), and nonparametric tests were applied. We considered a significance level α of 0.05.

Compliance with ethical standards. The study received approval from the institutional Ethics and Research Committee (CEIm Institut de Microcirurgia Ocular—IMO). All patients signed an institutional review board-approved informed consent. The study was conducted according to the tenets of the Declaration of Helsinki.

Results

Baseline data. Demographic and baseline patient data are presented in Table 1; individual patient data is presented in Supplementary Table 1. Of 291 consecutive DMEK surgeries, fourteen eyes of 13 patients (69.2% female) developed vs-CMO after DMEK (4.8% incidence); one of the eyes had persistent macular oedema before DMEK,which worsened after DMEK surgery (Fig. 1, Case #11). Mean patient age at the time of DMEK surgery was 63, 4 (10.3) years. Two patients (2/13, 15.4%) had known history of diabetes mellitus. Indication for DMEK was Fuchs corneal endothelial dystrophy (FECD) in 7 eyes (50.0%), pseudophakic bullous keratopathy in three eyes (21.4%), redo DMEK in two eyes (14.3%), phakic intraocular lens-related corneal decompensation in one eye (7.1%), and angle-closure glaucoma-related endothelial failure in one eye (7.1%). Eight eyes had axial length (AL) data, with a mean AL of 23.08 (1.55) mm and seven eyes had anterior chamber depth (ACD) data, with a mean ACD of3.37 (0.92) mm; of note,four eyes (28.6%) had shallow anterior chambers preoperatively, with three of them having history of iridotomy and one of them having history of acute angle-closure glaucoma. Three patients (3/13, 23.1%) had history of DMEK in the fellow eye. Five patients (5/13, 38.5%) had history of postoperative CMO in either the surgical eye or in the fellow eye; one of these patients had persistent, partially refractory postoperative CMEat the time of DMEK surgery. Four eyes (28.6%) had some ophthalmic comorbidity limiting visual potential after DMEK (one eye had macular drusen and angle-closure glaucoma, one eye had an epiretinal membrane, one eye was amblyopic, and one eye had glaucoma). Three eyes (21.4%) had staged DMEK surgery, preceded by cataract surgery less than 4 months before DMEK; the remainder underwent standalone DMEK surgery or DMEK graft exchange. After DMEK, re-bubbling was performed in two eyes (2/14, 14.3%), one of which underwent two re-bubbling procedures.

Patients' characteristics N = 14 eyes (13 patients)	
Demographic data	
Age, years	63.4 (10.3)
Female gender, n (%)	9/13 (69.2%)
Right eyes, n (%)	8/14 (57.1%)
Biometry data	
Anterior chamber depth, mm (n = 7)	3.37 (0.92)*
Axial length, mm (n = 8)	23.08 (1.55)
Ophthalmic history	
Ocular comorbidities, n (%)	4 (28.6%)
	Dry mild ARMD and glaucoma (1), ERM (1), Glaucoma (1),Amblyopia (1)
Previous corneal grafts, n (%)**	5 (35.7%)
	Interest eye (2), Fellow eye (3)
History of postoperative CMO, n (%)**	5 (35.7%)
	Interest eye (3), Fellow eye (2)
DMEK data	
Indication for DMEK (n, %)	FECD (7, 50.0%)
	PPBK (3, 21.4%)
	Redo DMEK (2, 14.3%)
	Glaucoma-related corneal decompensation (1, 7.1%)
	PIOL-related corneal decompensation (1, 7.1%)
Surgical technique (n, %)	Standalone DMEK (11/14, 78.6%)***
	Staged DMEK surgery (3/14, 21.4%)
Re-bubbling after DMEK, n (%)	2 (14.3%)

Table 1. Patient demographics and DMEK perioperative data. Quantitative variables are presented as mean (SD) or as median (P25-P75), depending on whether the variable followed a normal distribution. Categorical variables are presented as absolute and relative frequencies (n, %). *ARMD* age-related macular degeneration, *ERM* epiretinal membrane, *CMO* cystoid macular oedema, *DMEK* Descemet's membrane endothelial keratoplasty, *FECD* Fuchs' endothelial corneal dystrophy, *PPBK* pseudophakic bullous keratopathy, *PIOL* phakic intraocular lens. *Four eyes (28.6%) had shallow anterior chambers preoperatively, with three of them having history of iridotomy, of which one had history of acute angle-closure glaucoma. **Either in the interest eye or in the fellow eye. ***Two of the standalone DMEK surgeries were DMEK graft exchange.

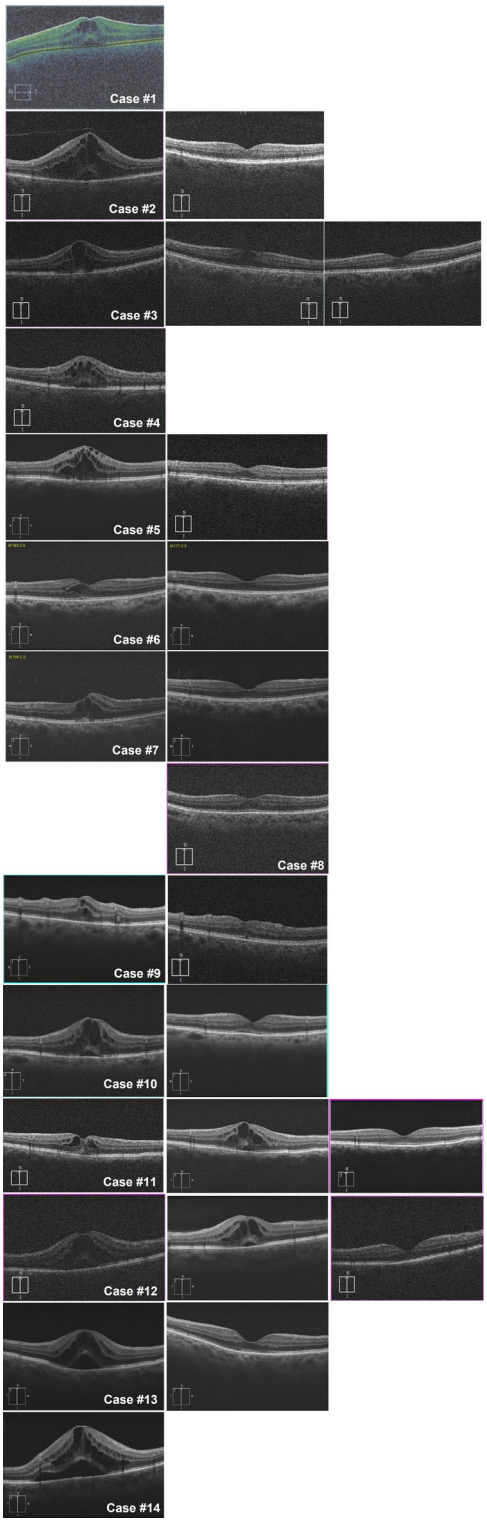


Figure 1. Macular spectral-domain optical coherence tomography (SD-OCT) images of the cases of postoperative visually significant cystoid macular oedema (vs-CMO). In Cases #3 and #12, SD-OCT scans at diagnosis of vs-CMO, before intravitreal corticosteroid injection, and after treatment are shown. In Case #11, CMO was present before DMEK, and worsening of macular oedema was observed after DMEK, improving after treatment. The SD-OCT image after treatment of vs-CMO was not available in the electronic medical records (EMR) of Case #1. Cases #4 and #14 had were lost to follow-up. Case #8 was diagnosed with vs-CMO, but the SD-OCT images were not available in the patient's EMRs.

In eyes without pre-existing CMO at the time of DMEK (n = 13), median time to detection of vs-CMO (T) was 4 (3–10) weeks; vs-CMO was detected during the first postoperative month in eight eyes (61.5%), and all cases vs-CMO were detected within the first 6 months after DMEK. Because patients referred for DMEK to our center are from a broad referral base, some patients performed SD-OCT elsewhere, and so OCT data before treatment was not available in our institution's EMRs for one case and the OCT data after treatment was not available in the EMRs of another case. The SD-OCT data analysis was thus performed in the cases where macular SD-OCT scans were retrieved from the patients' EMRs (Supplementary Table 1). In the cases where SD-OCT before and after treatment was retrieved from the patients' EMRs (n = 10), all eyes had intraretinal fluid, and six eyes (6/10, 60.0%) had subretinal fluid. There were two eyes with loss to follow-up (LTFU): one eye was lost to follow-up after diagnosis and so was not included in the success of treatment analysis; the second had persistent CMO at M4 post-DMEK under first-line treatment and was then LTFU, which we considered as a case of treatment failure. These cases were excluded from the BCVA and CRT analysis, and visual outcomes were reported for twelve eyes with successfully resolved CMO after treatment (12/13 eyes, 92.3%).SD-OCT macular scans available in the patients' EMRs are presented for all cases in Fig. 1.

Visual acuity and central retinal thickness outcomes. In eyes with resolution of CMO after treatment (n = 12), first-line treatment was effective in ten eyes (83.3%). Two eyes (16.7%) required second-line treatments with intravitreal CS (sustained-release 0.7-mg dexamethasone implant (Ozurdex, Allergan) in one case, and intravitreal injection of triamcinolone acetonide 40 mg/mL (Trigon Depot, Bristol-Myers-Squib) in another case). Both cases had resolution of CMO with full visual and anatomical recovery; however, the second eye had a complicated clinical course with rejection at M8 and IOL opacification requiring IOL exchange plus anterior vitrectomy, and eventually secondary graft failure at M21 post-DMEK.

In eyes with resolution of CMO after treatment (n = 12), there was a statistically significant improvement in median BCVA, from 0.60 (0.40–0.80) logMAR at the time of detection of vs-CMO to 0.30 (0.15–0.40) logMAR (p = 0.002, Wilcoxon signed rank test). Median time to resolution of vs-CMO was 3.0 (2.0–3.5) months. In eyes without eventual graft failure (n = 10), there was a statistically significant improvement in BCVA at last F-U observation (compared with baseline BCVA before DMEK surgery (0.02 (0.00–0.20) logMAR versus 0.58 (0.40–1.00) logMAR; p = 0.005, Wilcoxon signed rank test); all eyes reached final BCVA ≤ 0.30 logMAR (≥ 20/40 Snellen), 70% of eyes reached final BCVA ≤ 0.10 logMAR (≥ 20/25 Snellen), and 50% of eyes reached final BCVA ≤ 0 logMAR (≥ 20/20 Snellen).

CRT analysis was performed only in cases with SD-OCT images available before and after treatment of vs-CMO (n = 10) (Table 2). There was a statistically significant improvement in median CRT after treatment of vs-CMO, from 582.5 (400.0–655.0) μm at diagnosis of vs-CMO to 278.0 (258.0–294.0) μm (p = 0.005, Wilcoxon signed rank test).

Corneal clearing and DMEK graft survival. Of the eyes with resolution of CMO after treatment (n = 12), mean F-U time after DMEK surgery was 66.3 (32.0) months (range 18–126 months). At last F-U, ten eyes (10/12, 83.3%) had a clear cornea and a functioning DMEK graft. One eye (7.6%) had a complicated course after resolution of vs-CMO, with rejection at M8 and IOL exchange due to IOL opacification, with secondary graft failure 21 months after DMEK surgery. The other case had an immune rejection episode at 34-month follow-up, and graft failure was observed 66 months after DMEK.

Post-DMEK vs-CMO data and outcomes	
BCVA, logMAR (n = 12)	
BCVA before DMEK, logMAR (n = 12)	0.58 (0.35–0.85) logMAR
BCVA at diagnosis of vs-CMO, logMAR (n = 12)	0.60 (0.40–0.80) logMAR
BCVA after resolution of vs-CMO, logMAR (n = 12)	0.30 (0.15–0.40) logMAR
BCVA at last F-U, logMAR (n = 10)*	0.02 (0.00–0.20) logMAR
Macular SD-OCT data (n = 10)**	
CRT at diagnosis of post-DMEK vs-CMO, μm	582.5 (400.0-655.0) μm
Presence of IRF/SRF at diagnosis, n (%)	IRF 10 (100%)/SRF 6 (60%)
CRT after treatment vs-CMO, μm	278.0 (258.0–294.0) μm

Table 2. Visual outcomes and macular spectral-domain optical coherence tomography data after treatment of post-DMEK visually significant cystoid macular oedema. Quantitative variables are presented as mean (SD) or as median (P25-P75), depending on whether the variable followed a normal distribution. Categorical variables are presented as absolute and relative frequencies (n, %). *DMEK* Descemet's membrane endothelial keratoplasty, *vs-CMO* visually significant cystoid macular oedema, *BCVA* best-corrected visual acuity, *F-U* follow-up, *SD-OCT* spectral-domain optical coherence tomography, *CRT* central retinal thickness, *IRF* intraretinal fluid, *SRF* subretinal fluid. *BCVA analysis at last F-U excluding two eyes with graft failure. **SD-OCT data statistical analysis was only performed in patients where OCT scans were available before and after treatment of cystoid macular oedema.

Discussion

This is the first study to characterize the incidence and outcomes of postoperative vs-CMO after DMEK in the Iberic Peninsula. In our study, we have observed a 4.8% incidence of vs-CMO following DMEK, which is higher than our incidence of pseudophakic CMO but lower than our incidence of CMO after PKP (unpublished data). Our findings are in line with those of previous publications on EK and DMEK in particular (Table 3). In our study, we included eyes with comorbid conditions, which may be confounding factors in the limited postoperative visual acuity following DMEK. However, in these eyes CMO was considered as "visually significant" since there were not *de novo* changes in the preexisting comorbidities that would account for the "lower-than-expected postoperative visual acuity", and especially since visual acuity improved after CMO treatment in these cases. In our study, we have found that 60% of eyes had subretinal fluid in addition to intraretinal fluid cysts, higher compared with the reported incidence in previous studies[19,20]; we have observed no cases of isolated SRF, in agreement with the study by Flanary et al.[5]. The pathophysiologic mechanisms underlying postoperative CMO after EK is similar to that of pseudophakic CMO, with the additional release of inflammatory mediators due to iris manipulation by iridectomy and intracameral gas tamponade; one study found that iris damage before and after DMEK increased the risk of post-DMEK CMO[9], and preoperative LASER iridotomy may be associated with a lower risk of post-EK CMO[21]. In eyes that underwent DMEK, there is an increased concentration of pro-inflammatory mediators IFN-γ, IL-8, and IL-10 compared with eyes without signs of corneal disease scheduled for cataract surgery[22], and an amplified innate immune response (increased IL-5 and IL-8 levels) may play a role in failing DMEK grafts[23]; this pro-inflammatory milieu may explain the increased risk of post-DMEK CMO compared with cataract surgery in eyes without corneal endothelial disease. We have not quantified objectively the postoperative flare, which is a potential limitation of our study; objective measurements of postoperative intraocular inflammation (e.g. laser flare-cell photometry) could possibly provide further evidence of the role of inflammation in the pathophysiology of macular edema following EK.

Proposed strategies to decrease risk of post-EK CMO include: (1) recognition of preoperative risk factors for postoperative CMO; (2) possibly preoperative laser iridotomy[21], (3) early intensified postoperative topical CS therapy[19], and (4) possibly postoperative topical NSAIDs. Hoerster et al. compared two groups of DMEK patients who were treated with either topical CS 5 times daily vs topical CS hourly for the first postoperative week [19,] and found a 0% incidence of post-DMEK CMO in the hourly topical CS patient group, compared with a 12% incidence in the group receiving topical CS 5 times daily. Evidence for the potential benefit of postoperative NSAIDs comes from a previous study that found a protective effect of NSAID in preventing CMO after DSAEK[24], from extrapolation for published evidence regarding the effectiveness of NSAID for the prevention of pseudophakic CMO[16,25], and from indirect evidence by Inoda et al.[9], who found an increased risk of CMO after standalone DMEK compared with staged DMEK surgery, hypothesized to be due to the post-cataract surgery treatment which included topical NSAIDs. Although we did not perform a statistical analysis to compare the risk of CMO between staged DMEK and standalone DMEK, in our case series most patients had undergone standalone DMEK surgery rather than staged surgery.

As mentioned, the first strategy to decrease the risk of post-EK CMO is recognition of preoperative risk factors. However, several studies have analyzed preoperative and perioperative risk factors for CMO after EK, with conflicting findings. In our study, there was a relatively high proportion of non-FECD eyes, including two redo DMEK eyes, suggesting that indications other than FECD may represent a risk factor for vs-CMO. In several studies reporting CMO after EK (but not all), a relatively high proportion of cases occurred in non-FECD eyes[4,9,24], and previous studies have reported that glaucoma-related corneal endothelial dysfunction, and PPBK were risk factors for CMO after EK[7,17,18]; however, whether indication for DMEK is a risk factor for postoperative CMO remains unclear[3,4,9].

In our study, three eyes had history of DMEK in the fellow eye, however we do not believe that DMEK in the fellow eye was a contributing factor for vs-CMO after DMEK in the second eye[4,8]. Two eyes needed rebubbling after DMEK; while it is conceivable that rebubbling may increase the risk of post-EK CMO due to repeated manipulation and resulting in increased release of prostaglandins and other inflammatory mediators[9,20,26], this association has been disputed by other studies[3,4,6,8,19].

A high proportion of eyes that developed vs-CMO following DMEK in our study had previous history of pseudophakic CMO in the operated eye or in the fellow eye. Previous studies have excluded eyes with previous history of CMO from analysis, as this has been considered an uncontrollable risk factor for postoperative CMO[19]; however, we opted to include them in our study, since the main objective of our study was to analyze the outcomes of eyes with post-DMEK vs-CMO.

Although the findings by Myerscough et al. suggest that DMEK is associated with a 2.4-fold possibility of vs-CMO compared with DSAEK[4], we find it interesting to note that our incidence of vs-CMO after DMEK compares favorably with the reported incidence of vs-CMO following DSAEK in another study conducted in Spain[26], despite the limitations inherent to such a comparison.

In our study, most cases of vs-CMO developed during the first postoperative month after DMEK, and all cases developed vs-CMO within 6 months after DMEK. Reported average times to detection of post-EK CMO range from 5.2 weeks and 4.3 months [4, 6, 19, 26], with most cases appearing within the first month of surgery[3,5,9,20,24]. A standardized management protocol for postoperative CMO following EK is currently lacking. Proposed first-line approaches have included increased frequency of topical CS, topical NSAIDs, oral acetazolamide, and sub-Tenon CS injection, alone or in combination (Table 3). Our standard first-line treatment for post-DMEK vs-CMO consists of adding a topical NSAID 2id plus oral acetazolamide 250 mg 3id to the postoperative topical CS regime; in line with the work by Hoerster et al. showing that intensified topical CS in the early postoperative period reduce the risk of CMO[19], since two years we have also increased the frequency of topical CS during the first postoperative week to one drop every 2 hours, with close monitorization of IOP. This protocol appears

Author [REF]	Journal	Year of Publication	Country	EK eyes (n)	Type of EK graft	CMO eyes (n)	Fuchs' dystrophy in eyes with CMO (%)	Incidence of postoperative CMO	Average onset of CMO	Mean BCVA at diagnosis of CMO	Mean foveal thickness at diagnosis (μm)	Management of CMO	Additional treatment [Type, n]	Time to resolution of CMO	BCVA after treatment	Foveal thickness after treatment (μm)	Comments
Heinzelmann et al.[8]	Br J Ophthalmol	2015	Germany	155	DMEK	20	80.6%	13.00%	N/R		401	Topical prednisolone acetate 1%%	YES [Intravitreal injections anti-VEGF and triamcinolone, 1]	N/R			Eyes with shorter axial length had a higher risk of CMO following triple surgery; CMO after DMEK did not increase risk of post-DMEK CMO in the fellow eye
Hoerster et al.[19]	Am J Ophthalmol	2016	Germany	150	DMEK	9	98.0%	6.00%	5.2 ± 2.0 weeks	Mean BCVA decreased by 0.15 logMAR	507 ± 170 (100% had IRF / 22% had SRF)	Topical prednisolone acetate 1% q1H 1 week then tapered ± ACTZ 250 mg 2id 2wk in one patient	YES [intravitreal 0.7-mg dexamethasone implant, 1]	2.3 ± 1.2 months	Mean BCVA increased by 0.16 logMAR after initiation of therapy	349 ± 199	One eye had persitent CMO after 12 months despite Ozurdex treatment; Early intensified postoperative topical steroid therapy was effective prophylaxis for post-DMEK CMO
Flanary et al.[5]	Cornea	2016	USA	173	DMEK	13	93.1%	7.51% incidence of vs-CMO	All cases appeared within 1 month	N/R		Topical prednisolone acetate 1% 4id + Topical kerotolac 0.5% 4id	NO [0]	Within 6 months of treatment	All cases BCVA ≥ 20/30 and 69% ≥ 20/25	N/R	The incidence of vs-CMO after DMEK was similar in the setting of recent or remote cataract surgery
Quilendrino et al.[27]	Cornea	2017	The Netherlands	500	DMEK	5	89.2%	1.00%	N/R			Topical NSAID + Intensified topical CS ± ACTZ	YES [intravitreal injections anti-VEGF, 1]	N/R			80% of cases had staged surgery (cataract preceding DMEK up to 12 weeks)
Pedemonte-Sarrias et al.[26]	Int J Ophthalmol	2017	Spain	55	DSAEK	6	83.3%	10.91% incidence of vs-CMO	5.8 ± 4.3 weeks	N/R		Topical NSAID or Sub-Tenon CS ± Topical CS	YES [repeated sub-Tenon steroids, PPV, 1]	2.2 ± 1.7 months	N/R		One eye had persistent CMO; the incidence of CMO was higher with triple surgery compared with standalone DSAEK
Kocaba et al.[3]	Cornea	2018	France	74	DMEK	11	50.0%	14.86%	Most cases appeared between M1 and M3	0.30 logMAR	467	Topical indomethacine 0.1% 3id 2mo OR Topical dexamethasone/neomycin 3id 2mo + ACTZ 500 mg 3id	YES [Intravitreal 0.7-mg dexamethasone implant, 1]	N/R			Differences between standalone DMEK vs triple surgery not statistically significant
Kitazawa et al.[24]	Jpn J Ophthalmol	2018	Japan	334	DSAEK	18	55.6%	5.39%	All cases appeared within 1 month	N/R		Topical NSAIDs	NO [0]	1 month	0.39 logMAR	N/R	This group previously reported glaucoma-related corneal endothelial failure was a potential risk factor for post-DSAEK CMO [ref. 15]
Inoda et al.[9]	Cornea	2019	Japan	77	DMEK	12	32.0%	15.58%	All cases appeared within 1 month	N/R	542.4 ± 23.1	Topical bromfenac + Sub-Tenon injection triamcinolone acetonide	NO [0]	N/R	0.12 logMAR	N/R	Iris damage scores, air volume in the AC, simple DMEK and rebubbling were independent risk factors for post-DMEK CMO in Asian eyes
Ching et al.[6]	Curr Eye Res	2020	Canada	209	DMEK	8	92.8%	3.83% incidence of vs-CMO	8.9 ± 2.1 weeks	0.85 ± 0.52 logMAR	442 ± 149	Topical prednisolone acetate 1% + nepafenac	YES [Periocular triamcinolone, 2]	4.1 ± 1.7 months	0.17 ± 0.15 logMAR	274 ± 29	Differences between standalone DMEK vs triple surgery not statistically significant
Lohmann et al.[20]	Graefe Arch Clin Exp Ophthalmol	2021	Germany	107	DMEK	8	79.4%	7.48%	All cases appeared within 1 month	0.38 ± 0.92 logMAR	432.0 ± 97.6 (100% had IRF / 38% had SRF)	Topical nepafenac 1% 3id added to topical CS therapy until resolution, then tapered	NO [0]	N/R	0.14 ± 0.69 logMAR	297.5 ± 24.3	Rebubbling was significantly associated with CMO after uncomplicated DMEK in patients without systemic and surgery-related risk factors;
Myerscough et al.[4]	Br J Ophthalmol	2021	Italy	2233	DSAEK + DMEK	63	36.4%	2.82% incidence of vs-CMO (5.56% after DMEK / 2.36% after DSAEK)	4.3 ± 6.6 months	N/R		Topical Dexamethasone 0.1% 4id + Bromfenac 2id + ACTZ 500 mg 3id 1mo then taper 6mo	NO [0]	N/R			DMEK (OR 2.42), age > 67 years(OR 2.35), diabetes (OR 3.16) are independent risk factors for vs-CMO
Guindolet et al.[7]	Br J Ophthalmol	2021	France	246	DMEK	23	72.8%	9.36% incidence of vs-CMO	N/R	0.40 (0.16—0.52) logMAR	N/R	Topical keterolac and/or ACTZ 250 mg 3id in addition to topical CS	NO [0]	7 (4–11) months	0.15 (0.10—0.35) logMAR	N/R	History of ERM, PPBK, and intraoperative hyphaema were independent risk factors for vs-CMO; incidence of vs-CMO higher after standalone DMEK compared with triple surgery
Present study			Spain	291	DMEK	14	50.0%	4.8% incidence of vs-CMO	4 (3–10) weeks	0.60 (0.40–0.80) logMAR	582.5 (400.0–655.0) (100% IRF/60% SRF)	Add Topical NSAID 2id + ACTZ 250 mg 3id to topical CS regime	YES [Intravitreal CS, 2]	3 (2–3.5) months	0.30 (0.15–0.40) logMAR (all cases ≥ 20/40, and 50% ≥ 20/20)	278.0 (258.0–294.0)	See "Results" and "Discussion" sections

Table 3. Published results on the outcomes of postoperative cystoid macular oedema after endothelial keratoplasty. *EK* endothelial keratoplasty, *CMO* cystoid macular oedema, *BCVA* best-corrected visual acuity, *AC* anterior chamber, *DMEK* Descemet's membrane endothelial keratoplasty, *ACTZ* acetazolamide, *vs-CMO* visually significant cystoid macular oedema, *NSAID* non-steroidal anti-inflammatory drug, *CS* corticosteroid, *VEGF* vascular endothelial growth factor, *IRF* intraretinal fluid, *SRF* subretinal fluid, *DSAEK* Descemet stripping automated endothelial keratoplasty, *OR* odds-ratio; *ERM* epiretinal membrane, *PPBK* pseudophakic bullous keratopathy, *N/R* not reported.

to be an effective first-line approach for post-EK CMO, since most eyes achieved resolution of CMO within 2–6 months; second-line treatment consisting of intravitreal corticosteroid injection was successful in resolving CMO in those eyes with partial response to first-line treatment in the two cases we observed, although one of the eyes eventually had a complicated clinical course with rejection at M8 + IOL opacification requiring IOL exchange + anterior vitrectomy, and SGF at M21 post-DMEK. Median BCVA improved to 0.30 logMAR following resolution of CMO, and continuous improvement in BCVA was observed at last follow-up observation (median final BCVA 0.02 logMAR). In previous studies (Table 3), the prognosis of post-EK CMO was favorable in most patients, with resolution of macular edema and improvement in BCVA ranging between 0.12 and 0.39 logMAR; Hoerster et al. reported a mean 0.16 logMAR increase in BCVA after initiation of therapy[19]. In most published series, only very few cases required second-line treatments[3,6,8,19,26,27], and only two case series have reported cases of persistent CMO after EK, in which the authors reported refractory CMO despite second- and third-line treatments[19,26].The main limitation of our study is the presence ofcases of LTFU and cases of eyes where OCT data was not available in the patients' EMRs, which is a limitation of study's retrospective design. However, we highlight that the primary objectives of the study were to determine the proportion of eyes with vs-CMO after DMEK and the improvement in BCVA after treatment of vs-CMO, which are not affected by the missing data on CRT measurements.

In conclusion, this study reinforces the notion that postoperative vs-CMO is a relatively infrequent but potentially vision-threatening complication after DMEK surgery, and more frequent than pseudophakic CMO. Visual prognosis is good following treatment, with resolution of CMO with first-line treatment in a large proportion of cases. Although our study was not powered to determine risk factors for post-DMEK vs-CMO, we observed a high proportion of eyes that underwent DMEK for indications other than FECD, a high proportion of eyes with previous history of pseudophakic CMO, and that most eyes in our case series had undergone standalone DMEK rather than staged DMEK surgery. We believe that a standardized protocol for the management of post-EK CMO is needed, and future multicentric, prospective, randomized clinical trials are encouraged to ascertain the preoperative and perioperative risk factors for post-EK CMO, and to determine the most effective first- and second-line treatments for this postoperative complication.

Data availability

The datasets used and/or analyzed during the current study are available in the final version of the manuscript (Supplementary Table 1).

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Author contributions

N.M.-C.: conceptualization, methodology, research design, writing of the original draft, writing review and editing, data analysis. R.P.-V.: writing of the original draft, writing review and editing. I.S.-G.: data analysis, writing of the original draft. J.P.C.: writing of the original draft; writing review and editing, supervision, validation. A.D.-S.: writing review and editing, validation. F.M.: research design, data analysis, supervision, validation. J.G.: conceptualization, methodology, research design, writing of the original draft, supervision, validation.

Competing interests

The authors declare no competing interests.

Additional information

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Photorefractive keratectomy after DMEK for corneal decompensation by phakic IOL

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Abstract

Purpose: To provide the first description of photorefractive keratectomy (PRK) for the correction of mild residual refractive error after Descemet membrane endothelial keratoplasty (DMEK).

Methods: Case report.

Results: A 45 year-old woman presenting with phakic intraocular lens (PIOL)-related corneal decompensation underwent staged DMEK surgery following PIOL explantation and cataract surgery. Eighteen months after DMEK, uncorrected distance visual acuity (UDVA) was 20/60 and best-corrected visual acuity (BCVA) was 20/22, with a stable refraction. The patient requested refractive surgery to decrease spectacle dependance, and wavefront-optimized PRK was performed. At last follow-up observation thirty-three months after PRK (54 months after DMEK surgery), UDVA was 20/20, the cornea remained clear without signs of rejection or endothelial failure, and the endothelial cell loss rate was not accelerated after PRK.

Conclusion: Since long-term visual and refractive stability can be expected after DMEK, PRK may be a particular safe and effective approach for the correction of mild residual refractive errors after DMEK. However, we consider that surgeons must exercise caution when considering keratorefractive surgery in these eyes due to postoperative changes in corneal curvature and thickness, and further studies are encouraged.

Keywords

Photorefractive keratectomy, keratorefractive surgery, Descemet membrane endothelial keratoplasty

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Introduction

Phakic intraocular lens (PIOL)-related corneal decompensation is an increasingly frequent indication for Descemet's membrane endothelial keratoplasty (DMEK). These are patients who have high visual demands and high expectation of spectacle independence; this is also true in patients who undergo DMEK after refractive crystalline lens surgery. Although DMEK has been considered a refractive neutral procedure, endothelial keratoplasty is associated with mild hyperopic shift, with an overall mean change in spherical equivalent of +0.31 D and a mean change in astigmatism ranging from −0.60 to +1.11 D after DMEK.[1] Of note, DMEK may induce a refractive change ≥ 1.00 D in up to 35% of patients,[2] and up to 32% of patients experience a change in astigmatism higher than 1.00 D after DMEK, related to the

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combination of postoperative corneal deswelling and corneal incision-induced astigmatism.[3] However, long-term visual and refractive stability can be expected after DMEK, which has risen the question as to whether these cases are amenable to keratorefractive surgery, as has been reported in Descemet stripping endothelial keratoplasty.[4,5] This suggests that photorefractive keratectomy (PRK) may be a safer approach to correct the residual refractive error after DMEK.

We present the first reported case of wavefront-optimized photorefractive keratectomy (WFO-PRK) after DMEK. Written informed consent was obtained from the patient and the study was performed according to the tenets of the Declaration of Helsinki.

Case description

A 45 year-old female patient underwent staged DMEK for corneal decompensation due to accelerated endothelial cell loss and cortical cataract four years after implantation of an angle-supported, anterior chamber PIOL in another center for correction of −8.00 D myopia; DMEK was performed 8 weeks after combined PIOL explantation plus cataract extraction and pseudophakic IOL implantation. Manifest refraction at the time of DMEK surgery was −0.50 cyl @ 20°, with a best-corrected visual acuity (BCVA) of 0.52 logMAR (20/60 Snellen equivalent).

Postoperative cystoid macular edema was detected at 4-week follow-up after DMEK, which resolved after intravitreal sustained-release 700-µg dexamethasone implant. At 6-month follow-up after DMEK, BCVA was 0.10 logMAR (20/25 Snellen), with a residual refractive error of −0.50 sph −1.25 cyl @100°, and at 18-month follow-up BCVA was 0.04 logMAR (20/22 Snellen) with a stable manifest refraction, with uncorrected distance visual acuity (UDVA) of 0.52 logMAR (20/60 Snellen). The patient requested surgery to improve spectacle independence. Corneal topography showed a thinnest point of 472 µm, with keratometry 44.30 D and 45.80 D @45° (Figure 1). WFO-PRK was performed using the MEL 90 excimer LASER (Carl Zeiss Meditec, Jena, Germany), with a 6.0-mm optical zone diameter.

At the completion of the procedure, a therapeutic soft contact lens was placed for 5 days, during which topical ofloxacin was instilled q4 h in addition to a fixed combination of tobramycin 0.3% + dexamethasone 0.1% q4 h. After contact lens removal, postoperative treatment was, as our standard, consisting of fixed combination of tobramycin 0.3% + dexamethasone 0.1% q4 h during the first week and tapered over 3 weeks, then switched to fluorometholone 0.1% q8 h for 2 weeks with tapering over three months and then kept once daily indefinitely for post-DMEK rejection prophylaxis; a fixed combination of dexamethasone 0.05% + chloramphenicol 1% ointment q.h.s. for 3 months; and timolol 0.5% eyedrops q12 h for 3 months.

No postoperative complications were observed after PRK. Three weeks after PRK, UDVA was logMAR 0 (20/20 Snellen) with plano refraction, ant thirty-three months after PRK (54 months post-DMEK), UDVA was 0 logMAR (20/20 Snellen) and refraction remained plano. The cornea remained clear, without signs of allograft rejection or endothelial failure. Endothelial cell density (ECD) was 1704 cells/mm^2 (preoperative donor ECD decrease = 43%) one year after PRK, and 1045 cells/mm^2 (preoperative donor ECD decrease = 65%) at 54-month after DMEK (Figure 2), which is in agreement with the linear decrease in ECD in the medium to long-term after DMEK.[6]

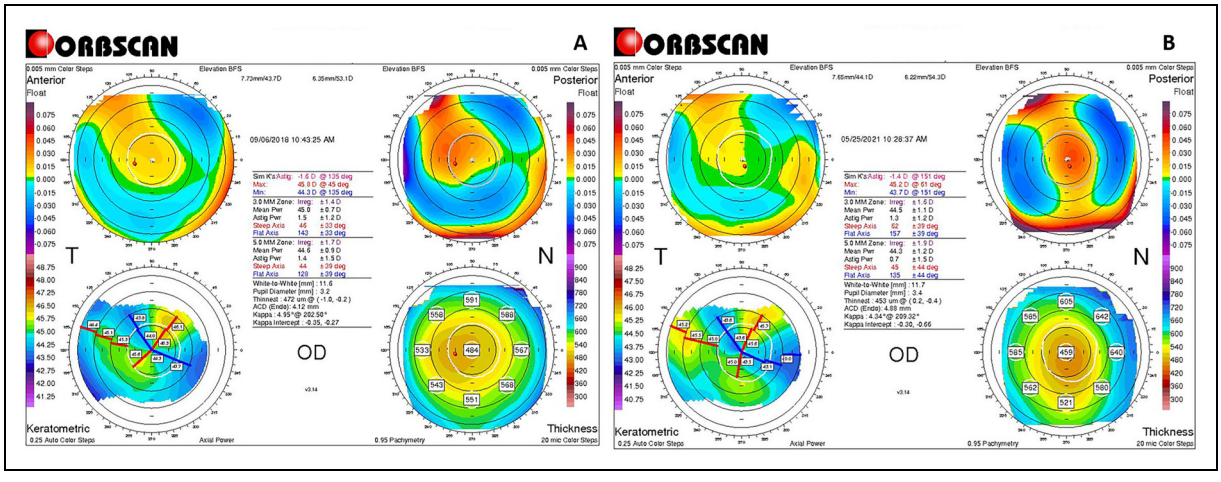


Figure 1. (A) Corneal topography before wavefront-optimized photorefractive keratectomy (PRK). (B) Corneal topography 33 months after PRK (54 months after DMEK), showing keratometric stability.

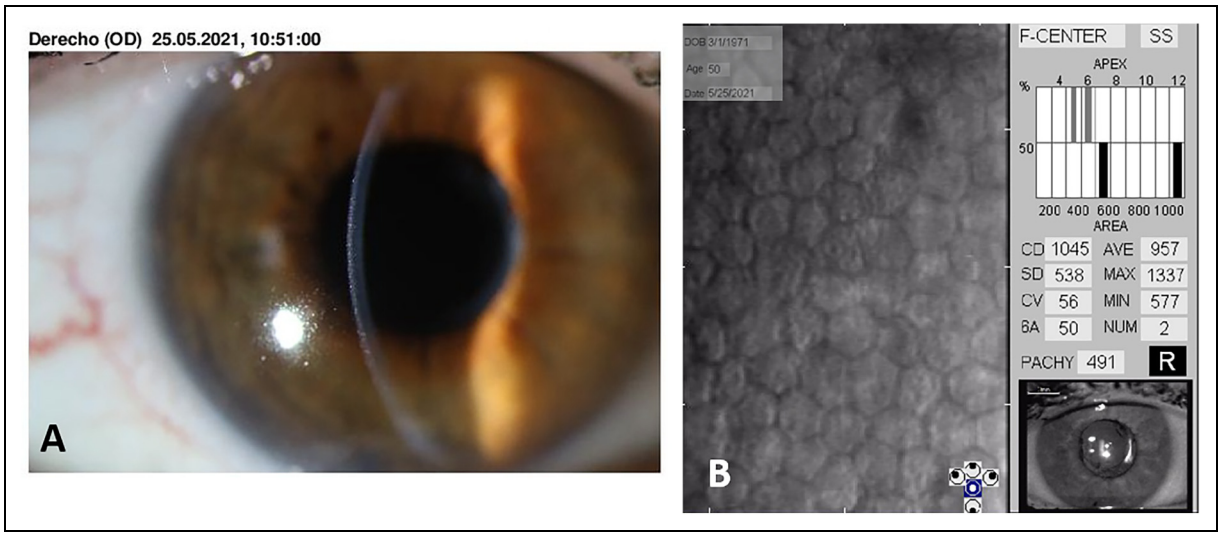


Figure 2. (A) Slit-lamp photograph showing corneal transparency maintained at last follow-up (54 months after DMEK). (B) Specular microscopy at last follow-up 33 months after photorefractive keratectomy, showing stable postoperative endothelial cell density.

Conclusions

Since the introduction of endothelial keratoplasty techniques, there has been an increasing interest in its refractive outcomes.[7] This is especially true in cases where DMEK is combined with refractive correction or cataract surgery, where the refractive target may be adjusted to account for the anticipated refractive shifts following DMEK. However, the literature is very limited regarding the treatment of post-DMEK refractive errors by means of laser refractive surgery. Price et al. reported the first case of laser-assisted in situ keratomileusis (LASIK) after DMEK, and raised doubt regarding the safety of excimer laser surgery in these eyes.[8] Since then, only one small case series reported the outcomes of femtosecond-assisted LASIK after DMEK in eyes with Fuchs' corneal endothelial dystrophy.[9] In that study, LASIK was found to be safe and effective.[9]

In our case, we have observed good midterm visual, refractive, and keratometric stability following PRK. To the best of our knowledge, this is the first published report of PRK for the correction of post-DMEK refractive error. Importantly, the DMEK graft ECD loss was not accelerated after PRK, in line with previous studies that donor graft ECD after DSAEK or DMEK is unlikely to be affected by excimer laser treatment.[4,9]

In eyes with refractive changes > 1.00 D following DMEK, the magnitude of refractive "surprise" reported in previous publications has ranged from 1.25 to 2.50 D in astigmatism, and nearly 90% of patients will be within 2.00 D of emmetropia. We believe that this amount of residual refractive error may be amenable to PRK in many cases. However, PRK may not be effective in all cases, and we still consider that surgeons must exercise caution when considering keratorefractive surgery in DMEK eyes. After DMEK, changes in both the anterior and posterior corneal curvatures can occur.[1] Resolution of corneal edema after DMEK may be associated with a thinner-than-normal central cornea, steeper pachymetric progression from the thinnest point to the periphery, and higher posterior elevation values.[10] Further long-term prospective studies are encouraged to adequately assess the stability of this surgery as well as the safety of the procedure.

Declaration of conflicting interests

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Authorship

Nuno Moura-Coelho: conceptualization, methodology, data collection, writing original draft, writing review and editing. Felicidad Manero: data collection, writing original draft, supervision, validation. Renato Papa: writing review and editing; Nicolas Amich: writing original draft; João P Cunha: writing review and editing, supervision, validation; José L Güell: conceptualization, methodology, project administration, writing review and editing, supervision, validation. All authors attest that the meet the current ICMJE criteria for authorship.

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REVIEW ARTICLE

Acute corneal allograft rejection following SARS-CoV-2 vaccination–A systematic review

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Abstract

All documented cases of acute corneal allograft rejection following SARS-CoV-2 vaccination were examined, to characterize possible risk factors and graft outcomes. Comprehensive search (4 electronic databases: PubMed, CENTRAL, ClinicalTrials.gov, Google Scholar, plus manual search in articles' reference lists) until March 1st 2022 to identify studies reporting acute corneal allograft rejection following SARS-CoV-2 vaccination; study protocol was developed in line with PRISMA statement. We analysed demographics, allograft type, rejection prophylaxis regime at the time of vaccination, transplantation-to-vaccination time (G-Vt), vaccination-to-immune reaction onset time (V-Rt), management, best-corrected visual acuity before and after rejection, and graft survival. Of 169 titles/abstracts screened, 16 studies (n = 36 eyes) met the inclusion criteria. Fourteen eyes (38.9%) had received >1 graft, and 11.1% of cases had history of immune reactions; 52.9% of cases occurred after the first dose. Median (P25-P75) G-Vt was 48 (10–78) months; median V-Rt was 9 (7–14) days. In eyes with resolved rejection, median time-to-resolution was 3 (1–4) weeks. Four eyes (11.1%) had partial resolution of corneal decompensation, and 5 grafts (13.9%) failed. Acute corneal allograft rejection after SARS-CoV-2 vaccination is a rare event, but may occur any time post-keratoplasty. Early recognition and prompt, aggressive treatment is warranted to optimize vision and graft survival. Well-known risk factors for rejection may be confounding factors, including the high proportion of cases with a history of previous grafts and the rejection prophylaxis regimes at the time of vaccination. Increasing immunosuppressants in the peri-vaccination period may decrease the risk of immune reactions, especially in high-risk cases.

KEYWORDS
coronavirus, keratoplasty, rejection, vaccines

1 | INTRODUCTION

Coronavirus disease (COVID-19), the ongoing pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is still a major public health challenge. The rapid development of a number of vaccines for SARS-CoV-2 was crucial for the prevention of severe manifestations of the disease and death due to COVID-19. SARS-CoV-2 has the potential to affect many tissues and systems, including ocular tissues and adnexa. (Cunha et al., 2020; Lin et al., 2021) The watchful control of adverse events (AEs) of the novel vaccines also led to the detection of rare ocular AEs after SARS-CoV-2 vaccination affecting any ocular structure and the optic nerve. (Y. K. Lee & Huang, 2021; Khan et al., 2021; Ng et al., 2022; Ng et al., 2021) Vaccination-induced corneal allograft rejection episodes have been anecdotally reported after vaccines against other infectious agents (E. H. Lee & Li, 2021) and recently reported after COVID-19 vaccination.

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The purpose of this systematic review was to examine all the documented cases of acute corneal allograft rejection following SARS-CoV-2 vaccination, and to characterize possible risk factors and graft outcomes after rejection.

2 | MATERIALS AND METHODS

2.1 | Setting

IMO Grupo Miranza Andorra, IMO Grupo Miranza Barcelona, NOVA Medical School | Faculdade de Ciências Médicas–Universidade Nova de Lisboa (NMS|FCM–UNL).

2.2 | Registration and search strategy

We conducted a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive electronic database search was done in four databases (PubMed, Cochrane Central Register of Controlled Trials [CENTRAL], Google Scholar, and ClinicalTrials.gov). Hand-search was also performed in reference lists of articles. The search strategy was meant to identify all studies reporting outcomes of acute corneal allograft rejection following SARS-CoV-2 vaccination, and was last run on March 1st, 2022.

2.3 | Eligibility criteria

Eligible studies included patients of any demographic who had acute corneal allograft rejection following SARS-CoV-2 vaccination, and analysed the resolution of the rejection episode after management. We included patients undergoing limbal and/or corneal transplantation.

Articles were included when the original research was published in English, and when at least 1 measurement at the time of diagnosed allograft rejection and 1 measurement after treatment of allograft rejection were reported.

Exclusion criteria were the following: (1) unpublished trials; (2) non-human studies or in vitro studies; (3) non-original studies; (4) publication languages other than English; (5) not full-text article; (6) absence of information of graft outcomes after management of the acute allograft rejection episode; (7) narrative or systematic reviews.

2.4 | Data management and collection

Two reviewers (NM-C, RP-V) independently screened the studies for eligibility, evaluated the quality and extracted the data according to PRISMA guidelines. Accuracy was confirmed by a third reviewer (JLG). Titles and abstracts were screened for inclusion criteria, and full-text articles were retrieved for all the references that met these criteria (Figure 1). Disagreements between reviewers were resolved by deliberation and consensus, and if needed, included an impartial third reviewer (JLG). Efforts to contact authors for further data were made whenever necessary.

Data were extracted from eligible studies according to PRISMA guidelines. Using forms with fields for the following: study first author, year of publication, journal of publication, study design, number of eyes and number of patients, baseline demographics, eligibility criteria, type of corneal and/or limbal allograft, time between corneal transplantation and SARS-CoV-2 vaccination (G-Vt), type of SARS-CoV-2 vaccine administered, number of SARS-CoV-2 vaccine doses received prior to the corneal allograft rejection episode, time between SARS-CoV-2 vaccination and corneal allograft rejection (V-Rt), potential confounding factors reported (including history of previous grafts, high-risk factors for corneal graft rejection, and immunosuppressive therapy at the time of SARS-CoV-2 vaccination) (Dua & Azuara-Blanco, 1999) management strategies for acute corneal allograft rejection, best-corrected visual acuity (BCVA) before SARS-CoV-2 vaccination, at the diagnosis of allograft rejection, and after resolution of the rejection, and corneal clearance after the rejection episode.

2.5 | Quality assessment

Studies were assessed for quality using the Quality Rating Scheme for Studies and Other Evidence ("JAMA Network Open—Instructions for Authors: Ratings of the Quality of the Vidence, n.d.") and by the BMJ Evidence-Based Medicine Tool for evaluating the methodological quality of case reports and case series proposed by Murad et al. (Murad et al., 2018) This is a tool that converged the previous criteria from Pierson, Bradford Hills and Newcastle Ottawa scale modifications into eight items that can be categorized into four domains (selection, ascertainment, causality, and reporting); the assessment of methodological quality was performed qualitatively, as proposed by Murad et al. (Murad et al., 2018). In the interest of simplification, we defined five qualitative categories (very good, good, average, poor, or very poor).

2.6 | Definition of outcomes

Our primary outcome was resolution of corneal graft rejection after treatment. We considered resolution of rejection as resolution of graft rejection signs following treatment as reported by the studies' authors (anatomical resolution) and/or as an improvement in BCVA following resolution of signs of rejection to at least 50% of the value of BCVA reported before the rejection episode (functional resolution). Additional outcomes were the following: final BCVA after corneal allograft rejection, central corneal thickness after allograft rejection, and graft survival after rejection.

3 | RESULTS

3.1 | Search results

Database search identified 195 records, resulting in 169 studies after duplicates were removed. Initial screening through title and abstract excluded 152

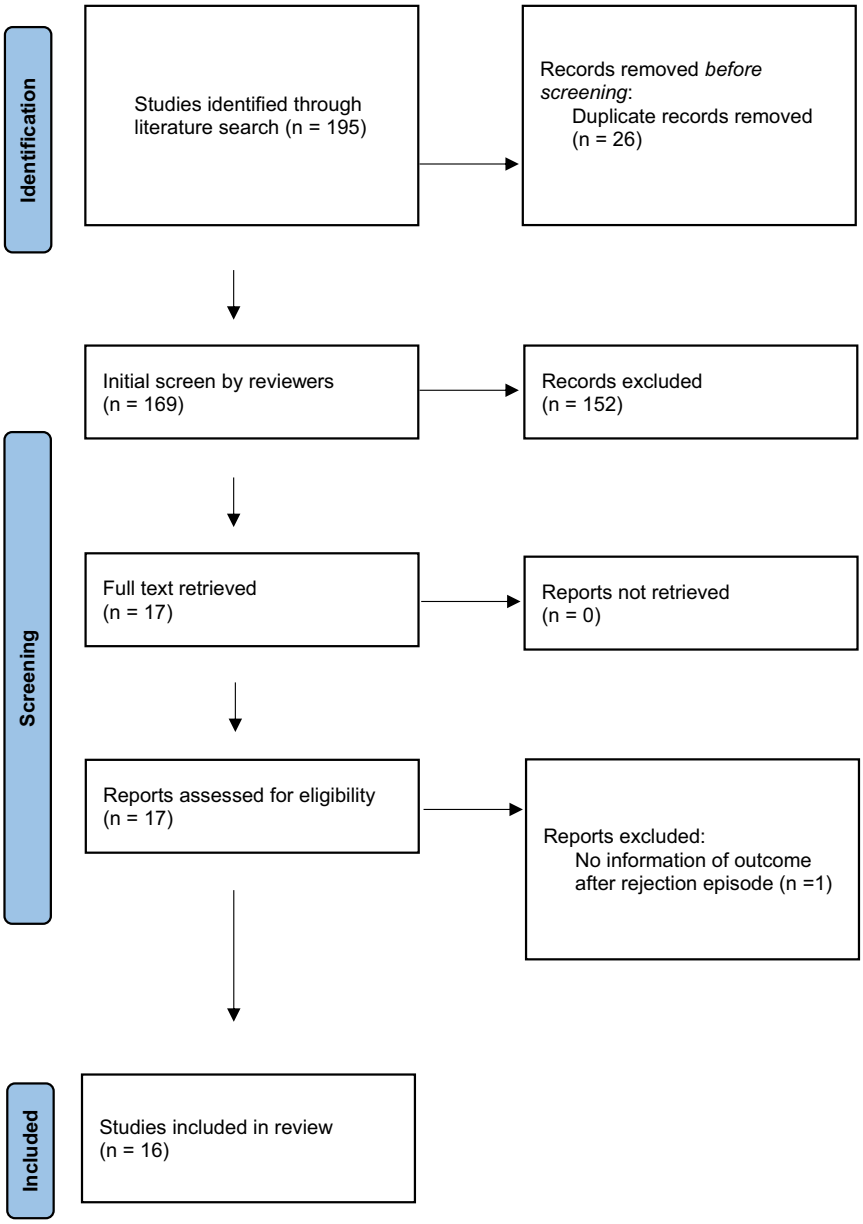


FIGURE 1 Preferred reported items for systematic reviews and meta-analyses (PRISMA) study flow diagram.

studies, leaving 17 papers for full-text assessment (Table S1). The case report by Ravichandran et al. (Ravichandran & Natarajan, 2021) was excluded, since it only presented information at the moment of diagnosis of acute corneal allograft rejection, without mentioning anatomical or functional outcomes after treatment, and so 16 studies were included in the review (Table 1). The PRISMA study flow diagram is presented in Figure 1.

Using the Quality Rating Scheme for Studies and Other Evidence ("JAMA Network Open—Instructions for Authors: Ratings of the Quality of the Vidence, n.d.), all studies received a rating of 4 or 5 (Table S2). Quality data analysis using the BMJ Evidence-Based Medicine Tool for evaluating the methodological quality of case reports and case series found that all studies analysed had at least "average" overall quality (Murad et al., 2018). All studies satisfied the selection domain (item 1), and the exposure was appropriately ascertained in all studies (item 2). All studies reported anatomical outcomes after acute corneal allograft rejection following SARS-CoV-2 vaccination (item 3 "was the outcome adequately ascertained?"), but the studies by Balidis et al., Fujimoto et al., and Gouvea et al. (Balidis et al., 2021; Fujimoto & Kiryu, 2021; Gouvea et al., 2022) did not report the visual outcomes (final BCVA), and the studies by Rajagopal et al. and Abousy et al. (Abousy et al., 2021; Rajagopal & Priyanka, 2022) did not report BCVA before the acute allograft rejection episode. Causality (item 4 alternative causes) was satisfactorily addressed in all studies, although the studies by Rajagopal et al., Balidis et al., Abousy et al., and Gouvea et al. (Abousy et al., 2021; Balidis et al., 2021; Gouvea et al., 2022; Rajagopal & Priyanka, 2022) failed to report the immune rejection prophylaxis regimes in some of their cases. Items 5 ("was there a challenge/rechallenge phenomenon?") and 6 (dose–response effect) of the tool were not included, as they did not apply to the studies analysed. All the cases had sufficient follow-up for outcomes to

TABLE 1 Studies included in the systematic review analysis of acute allograft rejection following SARS-CoV-2 vaccination

Author	Journal	Year	Type of publication	Eyes (*n*)	Patient (*n*)	Eyes (patients)
de la Presa	Cornea	2022	Case report	1	1	1 (1)
Yu	Cornea	2022	Case report	1	1	1 (1)
Shah	Cornea	2022	Case series	4	4	4 (4)
Molero-Senosiain	Cornea	2022	Case series	5	5	5 (5)
Gouvea	Cornea	2022	Case report	1	1	1
Simão	Cornea	2021	Case report	1	1	1 (1)
Rajagopal	IJO	2021	Case report	1	1	1 (1)
Parmar	IJO	2021	Case report	1	1	1 (1)
Balidis	EJO	2021	Case series	4	4	4 (4)
Nioi	Vaccines	2021	Case report	1	1	1 (1)
Abousy	Eye Contact Lens	2021	Case report	2	1	2 (1)
Fujimoto	J Ophthalm Res	2021	Case series	7	7	7 (7)
Wasser	Cornea	2021	Case report	2	2	2 (2)
Rallis	Eye Contact Lens	2021	Brief communication	1	1	1 (1)
Crnej	J Fr Ophthalmol	2021	Letter to the editor	1	1	1 (1)
Phylactou	Br J Ophthalmol	2021	Case series	3	2	3 (2)

occur (item 7), and all studies satisfied the reporting domain (item 8).

3.2 | Baseline demographics

A total of 36 eyes of 34 patients (46% females, mean age 65.1 ± 15.5 years) were included in this analysis (Table 2). Of these, 20 eyes (55.6%) had penetrating keratoplasty (PKP) graft rejection, 13 eyes (36.1%) had endothelial keratoplasty (EK) graft rejection (of which 6 were DMEK eyes and 7 were DSEK/DSAEK eyes), and 3 eyes (8.3%) had a rejection of limbal allografts (of which one was a case with combined PKP plus limbal stem cell transplant, one was an eye with primary keratolimbal allograft [KLAL] and subsequent PKP, and the other had a primary living-related conjunctival-limbal allograft); no cases of acute corneal allograft rejection following SARS-CoV-2 vaccination in eyes with anterior lamellar keratoplasty grafts were found in this analysis.

Fourteen eyes (38.9%) had received at least one previous allograft (Balidis et al., 2021; Dhillon et al., 2017; Gouvea et al., 2022; Molero-Senosiain et al., 2022; Parmar et al., 2021; Phylactou et al., 2021; Rajagopal & Priyanka, 2022; Rallis et al., 2021; Shah et al., 2022; Simão & Kwitko, 2022; Wasser et al., 2021; Yu et al., 2022) including redo PKP (6 eyes), (Balidis et al., 2021; Parmar et al., 2021; Simão & Kwitko, 2022; Wasser et al., 2021; Yu et al., 2022) PKP after limbal or sclerokeratoplasty grafts (2 eyes), (Gouvea et al., 2022; Shah et al., 2022) redo EK (4 eyes), (Balidis et al., 2021; Molero-Senosiain et al., 2022; Phylactou et al., 2021) and PKP after failed EK (2 eyes). (Rajagopal & Priyanka, 2022; Rallis et al., 2021) Two eyes had more than 3 corneal grafts (Molero-Senosiain et al., 2022; Simão & Kwitko, 2022) and four eyes (11.1%) had a history of previous rejection episodes (Abousy et al., 2021; Balidis et al., 2021; Molero-Senosiain et al., 2022; Simão & Kwitko, 2022).

3.3 | Rejection episode after SARS-CoV-2 vaccination

Median (P25-P75) G-Vt was 48 (10–78) months, ranging from 2 weeks (Phylactou et al., 2021) to 25 years after the transplant (Nioi et al., 2021). Immune suppressant regime information at the time of vaccination was reported in 29 eyes, six of which (20.7%) were off topical immunosuppressants; one eye that developed a rejection of a primary KLAL was in subtherapeutic doses of systemic tacrolimus (Gouvea et al., 2022). Eighteen cases (52.9%) of allograft rejection occurred after the first dose of the vaccine, and the remainder after the second dose. The type of vaccine was mRNA in 27 patients (79.4%), of which 19 cases were BNT162b2 vaccine (BioNTech, Pfizer), and 8 cases were mRNA-1273 vaccine (Moderna, NIAID). The type of vaccine was the non-replicating viral vector vaccine in 7 patients (21.6%), of which 4 had received the AZD1222 vaccine (ChAdOx1 nCoV-19, AstraZeneca), 1 had received the CoronaVac (Sinovac), and 2 had received the COVISHIELD™ ChAdOx1 nCoV-19 vaccine.

3.4 | Primary outcome

Resolution of rejection signs on the allograft (anatomical resolution) was reported in 28 eyes (77.8%), with five eyes (13.9%) evolving to allograft failure and three eyes (8.3%) showing partial anatomical improvement. When functional resolution was considered (based on improvement of BCVA to at least 50% of the BCVA before the acute allograft rejection episode), the rate of partial resolution increased to 11.1% due to one case reported by Molero-Senosiain et al. in which BCVA before rejection was 0.52 logMAR and final BCVA after anatomical resolution was 0.80 logMAR (Molero-Senosiain et al., 2022). Management strategies and outcomes of acute corneal

allograft rejection following SARS-CoV-2 vaccination are presented in Tables 3 and 4.

3.5 | Subgroup analysis

When analysis was performed for type of allograft (Tables 3 and 4), five out of 6 DMEK eyes (83.3%) had anatomical and functional resolution, with one case (16.7%) having only partial resolution of the corneal oedema (Balidis et al., 2021); five out of 7 DSEK/DSAEK grafts (71.4%) had anatomical and functional resolution, with one case (14.3%) of only partial resolution of the corneal oedema (Abousy et al., 2021) and one case (14.3%) (which was a redo DSAEK eye) evolving to DSAEK failure (Balidis et al., 2021).

About 15 out of the 20 PKP eyes (75%) had anatomical and functional resolution, with four eyes (20%) evolving to graft failure (Balidis et al., 2021; Fujimoto & Kiryu, 2021; Yu et al., 2022) and one eye (5%) with only partial resolution of the corneal oedema (Balidis et al., 2021). All cases of limbal allograft rejection resolved.

Of note, of the five eyes that evolved to graft failure after the acute rejection episode, three eyes were PKP grafts with a history of previous grafts (one eye was a redo PKP after a large diameter corneal graft (Yu et al., 2022), one was a tertiary PKP graft with history of rejection of the previous graft (Simão & Kwitko, 2022), and the other was a redo PKP (Balidis et al., 2021). The fourth eye was a redo DSAEK, and the fifth case was an eye that underwent primary PKP for herpetic endotheliitis without antiviral prophylaxis at the time of rejection (Fujimoto & Kiryu, 2021).

3.6 | Secondary outcomes

Median (P25-P75) V-Rt was 9 (7–14) days. Median (P25-P75) BCVA decreased from 0.30 (0.10–0.45) logMAR at the last observation before the rejection episode to 0.74 (0.48–1.68) logMAR at the moment of diagnosis of allograft rejection. Management strategies included starting topical corticosteroids (CS) or increasing the frequency of topical CS in all cases. The most frequently prescribed topical CS was dexamethasone 0.1% (13 cases), followed by prednisolone acetate 1% (6 cases), betamethasone 0.1% (4 cases), and difluprednate 0.05% (3 cases); the type of topical CS was not described in 7 cases (Molero-Senosiain et al., 2022; Phylactou et al., 2021; Rajagopal & Priyanka, 2022; Yu et al., 2022). Some corneal surgeons also added oral CS (de la Presa et al., 2022; Fujimoto & Kiryu, 2021; Molero-Senosiain et al., 2022; Parmar et al., 2021; Rajagopal & Priyanka, 2022; Wasser et al., 2021) and/or subconjunctival or intracameral CS to the treatment regime (Balidis et al., 2021). The eye with rejection of the KLAL graft was treated by increasing systemic tacrolimus to a therapeutic dosage.[14]

Median (P25-P75) corneal thickness at the time of acute allograft rejection was 716.5 (609.3–729.0) μm (Balidis et al., 2021; Fujimoto & Kiryu, 2021; Nioi et al., 2021; Phylactou et al., 2021; Rallis et al., 2021; Shah et al., 2022; Simão & Kwitko, 2022) and after resolution of the rejection, it improved to 610 (562.0–655.0) μm. (Balidis et al., 2021; Crnej et al., 2021; Nioi et al., 2021; Phylactou et al., 2021; Rallis et al., 2021; Shah et al., 2022) In eyes with resolved rejection, the median (P25-P75) time-to-resolution was 3 (1–4) weeks.

4 | DISCUSSION

This review of the available reports has found that acute corneal allograft rejection after SARS-CoV-2 vaccination is a rare event, considering the mass vaccination strategy adopted worldwide to achieve the so-called "herd immunity". A global database of COVID-19 vaccinations showed that by March 1, 2022, over 4 billion people had received the complete initial COVID-19 vaccination protocol worldwide, representing 9.39 billion doses (Mathieu et al., 2021). The current estimated prevalence of acute corneal allograft rejection following SARS-CoV-2 vaccination (calculated by dividing the number of events reported until March 1, 2022, by the number of doses administered up to March 1, 2022) would be 0.004 per million doses, which is 10 times lower than previously reported by Wang et al. (Wang et al., 2022) The association between SARS-CoV-2 vaccination and acute corneal allograft rejection episodes is inferred in the published reports by the temporal association, and by the evidence of previous reports of acute rejection episodes following vaccination for other infectious agents (Lee & Li, 2021; Solomon & Frucht-Pery, 1996; Steinemann et al., 1988; Vignapiano et al., 2021; Wertheim et al., 2006; Matoba, 2022); however, these cases are anecdotal, and no statistical association has been proven between vaccination and corneal allograft immune reactions. It has been suggested that vaccinations may trigger inflammatory responses through the development of cross-reactivity with cellular antigens or because of a non-specific immune activation (Lockington, 2021). Proposed mechanisms for acute corneal allograft rejection following SARS-CoV-2 vaccination include the activation of toll-like receptors on the ocular surface and CD4+ T helper-1 cell (Th1) immunity (Ng et al., 2022), and the reduction of the corneal immune privilege due to systemic immune dysregulation (Steinemann et al., 1988). While this mechanism has been better characterized for PKP, it has been less precisely described for EK grafts (Hos et al., 2019); it has been proposed that innate cellular responses or non-cellular rejection mechanisms independent of this classic Th1 mechanisms involved in PKP rejection may be relevant in EK endothelial cell loss and rejection (Luznik et al., 2019).

The analysis of the reported cases of acute corneal allograft rejection following SARS-CoV-2 vaccination shows that a high proportion of eyes had some risk factors for allograft rejection, with approximately 40% of eyes having a history of previous corneal grafts, approximately 11% of eyes having a history of rejection episodes, and nearly 20% of eyes being off any topical immunosuppressants at the time of vaccination. The Collaborative Corneal Transplantation Studies reported an additional 15% of immune reaction episodes (rejection episodes) for

TABLE 2 Baseline demographics and SARS-CoV-2 vaccination data

Author	Eyes (patients)	Gender/age (years)	Race	Transplant	History of previous graft
de la Presa	1 (1)	F/27	N/R	Primary LR-CLAL	No
Yu	1 (1)	M/51	N/R	Redo PKP, large diameter graft	Yes
Shah	4 (4)	M/74	Caucasian	Unilateral DMEK	No
		F/61	Caucasian	Unilateral sclerokeratoplasty + PKP	Yes
		F/69	African American	DSAEK	No
		M/77	Caucasian	PKP	No
Molero-Senosiain	5 (5)	F/72	Caucasian	Redo DSAEK (third graft)	Yes
		F/82	Caucasian	Primary DSAEK	No
		M/55	Asian	Primary PKP	No
		M/61	Caucasian	Primary PKP	No
		F/48	Caucasian	Primary PKP	No
Gouvea	1	M/72	N/R	Primary KLAL + subsequent PKP	Yes
Simão	1 (1)	F/63	Asian	Redo PKP (third graft)	Yes
Rajagopal	1 (1)	M/79	N/R	PKP after failed DSEK	Yes
Parmar	1 (1)	M/35	Indian	Redo PKP	Yes
Balidis	4 (4)	F/77	Caucasian	Redo DMEK	Yes
		F/63	Caucasian	Redo PKP	Yes
		M/69	Caucasian	Primary PKP	No
		M/63	Caucasian	Redo DSAEK	Yes
Nioi	1 (1)	F/44	Caucasian	Primary PKP	No
Abousy	2 (1)	F/73	N/R	Primary DSEK	No
				Primary DSEK	No
Fujimoto	7 (7)	M/80	N/R	Primary PKP	No
		F/32	N/R	PKP+LSCT	No
		M/50	N/R	Primary PKP	No
		M/55	N/R	Primary PKP	No
		F/92	N/R	Primary PKP	No
		M/87	N/R	Primary PKP	No
		M/84	N/R	Primary DSAEK	No
Wasser	2 (2)	M/73	N/R	Redo PKP	Yes
		M/56	N/R	Redo PKP	Yes
Rallis	1 (1)	F/68	N/R	PKP after failed DSAEK	Yes
Crnej	1 (1)	M/71	N/R	Primary DMEK	No
Phylactou	3 (2)	F/66	Caucasian	Primary DMEK	No
		F/83	Caucasian	Primary DMEK	No
				DMEK after failed DSAEK	Yes

Abbreviations: COVISHIELD, ChAdOx1nCoV-19 Corona Virus Vaccine Recombinant COVISHIELD; CsA, cyclosporine A; Dexa, dexamethasone; DMEK, Descemet membrane endothelial keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty; DSEK, Descemet stripping endothelial keratoplasty; F, female; FML, fluorometholone; G-Vt, time between graft and vaccination; KLAL, keratolimbal allograft; LR-CLAL, living-related conjunctival-limbal allograft; LSCT, limbal stem cell transplantation; M, male; MMF, mycophenolate mofetil; N/R, not reported; PDN, prednisolone; PKP, penetrating keratoplasty; V-Rt, time between vaccination and immune reaction episode.

History of immune reaction episodes	G-Vt (months)	Immunosuppressants at the time of vaccination	SARS-CoV-2 vaccine	Doses (*n*)	V-rt (days)
No	55	MMF 500 mg day + PDN 1% 2id	Moderna	1	15
No	0.75	Topical CS 4id	Moderna	1	3
No	5	Topical FML 0.1% 1id	Moderna	1	7
No	30	PDN 1% 1id	Moderna	2	7
No	72	PDN 1% 1id	Moderna	2	14
No	264	Inconsistent use of topical steroids	Moderna	2	7
No	48	Dexa 0.1% 4id	Pfizer	1	14
No	48	Off steroids 2 years before vaccination	Pfizer	1	14
No	104	0	AZD1222	2	7
No	240	N/R	AZD1222	2	28
Yes	48	Dexa 0.1% 1id	Pfizer	1	28
No	78	Systemic Tacrolimus subtherapeutic	Pfizer	2	30
Yes	84	0.03% Tacrolimus, off steroids 2 years before vaccination	CoronaVac	1	1
No	48	0	COVISHIELD	2	42
No	6	PDN 1% 1id + CsA 0.05% 2id	COVISHIELD	1	4
Yes	12	Dexa 0.1% + oral valacyclovir	Moderna	1	7
No	24	N/R	Moderna	2	7
No	22	N/R	AZD1222	1	5
No	9	Topical Dexa 1id	AZD1222	1	10
No	300	N/R	Pfizer	1	13
Yes	96	N/R	Pfizer	2	4
No	96	N/R			9
No	Mean 687.4 ± 647.5 days (22.9 ± 21.6 months) (range 6.7–68.5 months)	FML 0.1% 4id	Pfizer	2	46 from 1st dose
No		Betamethasone 0.1% 4id + Tacrolimus 0.1% 2id	Pfizer	2	87 from first dose
No		Betamethasone 0.1% 6id + Tacrolimus 0.1% 2id	Pfizer	2	102 from first dose
No		0	Pfizer	1	14
No		Betamethasone 0.1% 4id	Pfizer	2	111 from 1st dose
No		Betamethasone 0.1% 2id	Pfizer	2	82 from 1st dose
No		FML 0.1% 2id	Pfizer	2	41 from 1st dose
No	24	Dexa 0.1% 1id	Pfizer	1	13
No	10	Off steroids 4 months before vaccination	Pfizer	1	14
No	4	PDN 0.5% 4id	Pfizer	1	4
No	5	N/R	Pfizer	1	7
No	0.5	Dexa 0.1% 4id	Pfizer	1	7
No	72	Off steroids 6 months before vaccination	Pfizer	2	21
No	36				

TABLE 3 Management and outcomes of endothelial keratoplasty after acute corneal allograft rejection following SARS-CoV-2 vaccination

Author	Type of EK allograft	Management	Graft outcome	Time-to-resolution (weeks)
Shah	Primary DMEK	Topical PDN 1% q2h	Resolution of acute rejection episode	5
	Primary DSAEK	Topical Difluprednate 0.05% 6id	Resolution of acute rejection episode	3
Molero-Senosiain	Redo DSAEK (third graft)	Topical Dexa 0.1% q1H	Resolution of acute rejection episode	3
	Primary DSAEK	Intensive topical CS non-specified	Resolution of acute rejection episode	3
Balidis	Redo DMEK	Subconjunctival Dexa + topical Dexa 0.1% q2h	Worsening requiring IV CS and topical Dexa 0.1% q1h, started improvement at 4 weeks	Partial resolution
	Redo DSAEK	Topical Dexa q2h + hypertonic ointment	Failed DSAEK graft	Failed
Abousy	Primary DSEK	Topical PDN 1% 4id	At 4 weeks required topical PDN 1% q1h + ointment (20/80). Partial resolution of corneal oedema	Partial improvement
	Primary DSEK	Topical PDN 1% 4id	At 4 weeks required topical PDN 1% q1h + ointment (20/150). Resolution of acute rejection episode	8
Fujimoto	Primary DSAEK	Topical Betamethasone 0.1% 4id + Tacrolimus 0.1% 2id	Resolution of acute rejection episode	N/R
Crnej	Primary DMEK	Topical Dexa 0.1% q2h + Oral valacyclovir 1 g q8h	Resolution of acute rejection episode	1
Phylactou	Primary DMEK	Topical Dexa 0.1% q1h	Resolution of acute rejection episode	1
	Primary DMEK	Topical CS q1h	Resolution of acute rejection episode	1
	DMEK after failed DSAEK	Topical CS q1h	Resolution of acute rejection episode	1

Abbreviations: BCVA, best-corrected visual acuity; CS, corticosteroid; Dexa, dexamethasone; DMEK, Descemet membrane endothelial keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty; DSEK, Descemet stripping endothelial keratoplasty; EK, endothelial keratoplasty; IV, intravenous; MPDN, methylprednisolone; N/A, not applicable; N/R, not reported; PDN, prednisolone.

each additional PKP graft (Maguire et al., 1994). These are potentially confounding factors in the interpretation of the relationship between association, correlation, and causation.

Importantly, reported immune reactions after COVID-19 vaccination occurred at any time after keratoplasty, anywhere from 14 days to 25 years after surgery. Management strategies for the prevention of acute rejection episodes after vaccination are not consensual amongst corneal surgeons, and nearly half of corneal specialists do not alter management in the setting of keratoplasty and vaccinations. However, there is an overall attitude towards increasing topical CS in the peri-vaccination period, particularly in patients with recent EK surgery, and towards topical CS coverage in high-risk PKP scenarios (Lockington et al., 2021). We believe that increasing immunosuppressant prophylaxis in the vaccination period may decrease the risk of acute rejection episodes, especially in high-risk cases (Moura-Coelho et al., 2021). All patients with corneal allografts should be regularly reminded of the clinical symptoms of rejection and advised to seek urgent review to start treatment promptly (Lockington, 2021); in our clinical practice, the patients are taught the mnemonic "RSVP" for redness, sensitivity to light, vision blurring, and pain. (Moura-Coelho et al., 2021). We also remind general ophthalmologists that any inflammation in an eye with a prior corneal graft should be suspected of being graft rejection until proven otherwise.

A larger number of cases of acute corneal allograft rejection following SARS-CoV-2 vaccination were treated with topical dexamethasone, compared with the number of patients that were treated with topical prednisolone. These findings contrast slightly to the practice patterns previously reported by Kharod-Dholakia et al. (Kharod-Dholakia et al., 2015), where prednisolone was reported as the drug of choice for the management of allograft rejection.

While the prognosis for BCVA and for graft survival were good overall, 25% of the PKP eyes with acute corneal allograft rejection following SARS-CoV-2 vaccination had incomplete resolution or graft failure, and although the risk of graft failure due to rejection after EK is relatively low (Price et al., 2018; Stulting et al., 2018) as many as 20–25% of EK eyes may be at risk of decreased corneal transparency or graft failure due to immune reaction after SARS-CoV-2 vaccination.

BCVA at last observation before immune reaction (logMAR)	BCVA at diagnosis of immune reaction (logMAR)	Final BCVA (logMAR)	Corneal thickness before immune reaction (µm)	Corneal thickness at immune reaction (µm)	Final corneal thickness (µm)
0.10	0.48	0.30	N/R	743	655
0.10	0.40	0.20	N/R	719	633
0.42	0.60	0.48	N/R	N/R	N/R
0.3	0.70	0.50	N/R	N/R	N/R
N/R	N/R	N/R	N/R	720	710
0.30	1.9	N/A (failed graft)	N/R	N/R	N/R
N/R	0.54	0.40	N/R	N/R	N/R
N/R	0.3	0.10	N/R	N/R	N/R
0.22	0.3	N/R	641	724	N/R
0.18	0.8	0.10	N/R	714	512
0.00	0.78	0.00	525	652	526
0.00	0.60	0.00	N/R	N/R	N/R
0.00	0.30	0.00	N/R	N/R	N/R

The main strengths of our study are: (1) Our database search enabled us to find the largest number of reported cases (more than the previous summary of evidence), (Wang et al., 2022) and is the only study summarizing evidence including published data in 2022, being the most up to date database search available; and (2) we provide an in-depth analysis of potentially confounding factors and of the clinical outcomes of acute corneal allograft rejection following SARS-CoV-2 vaccination. The main limitation of this review is the fact that only case reports or small case series were found in the literature search. Another important limitation is that the number of publications on acute rejection after SARS-CoV-2 vaccination exceeds by far the number of reports of keratoplasty patients developing corneal allograft rejection after other vaccines; while this is possibly due to increased awareness of the potential of immunization-induced immune reactions on corneal grafts, it is also possible that the novelty of the viral agent and the novelty of the mRNA vaccines raised a potential publication bias. We emphasize our belief that the benefits of SARS-CoV-2 vaccination far outweigh the potential risks of acute corneal allograft rejection following vaccination, considering the potentially severe complications of COVID-19 disease, and considering the potential ocular manifestations of COVID-19 (Cunha et al., 2020), which may also include acute corneal graft rejection (Ang et al., 2020; Behera et al., 2021; Jin & Juthani, 2020; Singh & Mathur, 2021). Most corneal surgeons agree with this policy, according to a recent survey of 142 corneal surgeons (Lockington et al., 2021).

In conclusion, acute corneal allograft rejection following SARS-CoV-2 vaccination is a rare event, but may occur at any time post-transplantation and may threaten vision and graft survival. Well-known risk factors for allograft rejection may be confounding factors for post-vaccination immune reactions. Early recognition of symptoms and signs of acute rejection and prompt, aggressive treatment is warranted to optimize vision and graft survival. Increasing immunosuppressants in the peri-vaccination period may decrease the risk of acute rejection episodes, especially in high-risk cases.

TABLE 4 Management and outcomes of penetrating keratoplasty grafts and limbal allografts after acute corneal allograft rejection following SARS-CoV-2 vaccination

Author	Transplant	Management	Graft outcome	Time-to-resolution (weeks)
de la Presa	Primary LR-CLAL	Difluprednate 0.05% q1h + PDN 30 mg day	Resolution of acute rejection episode	4
Yu	Redo PKP, large diameter graft	Topical CS q2H	Graft failure	N/A (failed graft)
Shah	Unilateral sclerokeratoplasty + PKP	Topical PDN 1% q1h	Resolution of acute rejection episode	6
	PKP	Topical PDN 1% 5id	Resolution of acute rejection episode	1
Molero-Senosiain	Primary PKP	Intensive topical CS non-specified	Resolution of acute rejection episode	3
	Primary PKP	Intensive topical CS non-specified + IV MPDN 3 pulses 500 mg q48h	Resolution of acute rejection episode	2
	Primary PKP	Topical Dexa 0.1% q1H	Resolution of acute rejection episode	1
Gouvea	Primary KLAL + subsequent PKP	Topical Difluprednate 0.05% q1H + Increased Systemic tacrolimus 2 mg 2id	Resolution of acute rejection episode	16
Simão	Redo PKP (third graft)	Topical Dexa q1H + polydimethylsiloxane 4id + timolol + bimatoprost	Partial resolution, recurrence 1 month after (2nd dose of vaccine) leading to graft failure	N/A (failed graft)
Rajagopal	PKP after failed DSEK	Topical CS q1h + Oral CS	Resolution of corneal oedema, with mild residual stromal haze	8
Parmar	Redo PKP	Topical PDN 1% q1H + atropine 1% 3id + intravenous MPDN bolus 3 days 3 g then oral PDN 60 mg/day	Resolution of acute rejection episode	3
Balidis	Redo PKP	Topical CS q1h + Intracameral CS	Unresolved corneal oedema	N/A (failed graft)
	Primary PKP	Topical CS + Oral CS + Subconjunctival dexa	Partial resolution	Partial improvement
Nioi	Primary PKP	Topical Dexa 0.2% q1h + cholecalciferol 1000 IU daily	Recurrence at 8-week, resolved with reintroduction of topical steroids	4
Fujimoto	Primary PKP	Topical Betamethasone 0.1% 6id + Acyclovir ointment 5id	Graft failure	N/A (failed graft)
	PKP + LSCT	Topical FML 0.1% q1H	Resolution of acute rejection episode	N/R
	Primary PKP	Add oral PDN 20 mg/day	Resolution of acute rejection episode	N/R
	Primary PKP	Topical FML 0.1% q1H	Resolution of acute rejection episode	N/R
	Primary PKP	Topical Betamethasone 0.1% 4id	Resolution of acute rejection episode	N/R
	Primary PKP	Topical Betamethasone 0.1% 4id	Resolution of acute rejection episode	N/R
Wasser	Redo PKP	Topical Dexa 0.1% q1h + Oral PDN 60 mg	Resolution of acute rejection episode	1
	Redo PKP	Topical Dexa 0.1% q1h + Oral PDN 60 mg	Resolution of acute rejection episode	2
Rallis	PKP after failed DSAEK	Topical Dexa 0.1% q1h + Oral acyclovir 400 mg 5id	Resolution of acute rejection episode	3

Abbreviations: BCVA, best-corrected visual acuity; CS, corticosteroid; Dexa, dexamethasone; DMEK, Descemet membrane endothelial keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty; DSEK, Descemet stripping endothelial keratoplasty; IV, intravenous; KLAL, keratolimbal allograft; LR-CLAL, living-related conjunctival-limbal allograft; LSCT, limbal stem cell transplantation; MPDN, methylprednisolone; N/A, not applicable; N/R, not reported; PDN, prednisolone; PKP, penetrating keratoplasty.

BCVA at last observation before immune reaction (logMAR)	BCVA at diagnosis of immune reaction (logMAR)	Final BCVA (logMAR)	Corneal thickness before immune reaction (µm)	Corneal thickness at immune reaction (µm)	Final corneal thickness (µm)
0	0.00	0.00	N/R	N/R	N/R
1.30	2.30	N/A (failed graft)	N/R	N/R	N/R
0.30	0.60	0.48	N/R	752	610
0.10	0.48	0.30	N/R	N/R	N/R
0.52	1.90	0.80	N/R	N/R	N/R
0.7	1.24	0.80	N/R	N/R	N/R
0.36	1.90	0.70	N/R	N/R	N/R
0.54	0.6	N/R	N/R	N/R	N/R
0.40	1.00	N/A (failed graft)	507	841	N/R
N/R	0.78	0.78	N/R	N/R	N/R
0.78	1.80	0.18	N/R	N/R	N/R
0.10	0.80	N/A (failed graft)	470	585	N/R
N/R	N/R	N/R	535	757	660
0.18	1.90	0.18	560	692	562
0.40	1.30	N/A (failed graft)	584	726	N/R
0.04	0.30	N/R	552	649	N/R
2.3	2.4	N/R	493	536	N/R
0	0.48	N/R	512	586	N/R
0.3	0.4	N/R	506	596	N/R
0.3	0.4	N/R	459	561	N/R
0.60	1	0.60	N/R	N/R	N/R
0.10	2	0.10	N/R		N/R
0.48	1.90	0.30	N/R	730	609

AUTHOR CONTRIBUTION

Nuno Moura-Coelho: conceptualization, methodology, research design, writing of the original draft, writing review and editing, data analysis. João Paulo Cunha: data analysis, writing review and editing, supervision, validation. Renato Papa: data analysis, writing of the original draft. Óscar Gris: supervision, validation. José Güell: conceptualization, methodology, research design, writing review and editing, supervision, validation.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Ultrathin DSAEK versus DMEK – Review of systematic reviews

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Abstract

The efficacy and safety of Descemet's membrane endothelial keratoplasty (DMEK) and ultrathin Descemet stripping automated endothelial keratoplasty (UT-DSAEK) have been recently compared in several systematic reviews (SRs). The aim of this study was to assess the evidence quality of such SRs, in order to obtain a scientifically rigorous comparison between the two techniques. We performed a systematic review of SRs and meta-analyses comparing the efficacy and safety between UT-DSAEK and DMEK up to 24th March 2023, using 3 electronic databases (PubMed, Cochrane Library, Google Scholar) plus manual reference search. Specific outcomes analyzed included best-corrected visual acuity (BCVA), endothelial cell density (ECD), rebubbling rate, and other postoperative complications. Of 90 titles/abstracts screened, four SRs met the inclusion criteria. All SRs adequately analyzed potential bias of the included studies. One SR raised concern for potential literature search bias and two SRs have heterogeneity in some outcomes analyzed. All SRs found higher BCVA after DMEK, but one SR reported significant heterogeneity. All SRs found significant heterogeneity in ECD analysis, with one SR providing inconsistent analysis of this outcome. Three SRs analyzed rebubbling rates, favoring UT-DSAEK over DMEK. Three SRs concluded a higher overall complication rate after DMEK, although rebubbling may be a confounding factor. This systematic review clarifies the strengths and weaknesses of published SRs and reinforces the conclusion that DMEK leads to superior visual outcomes compared to UT-DSAEK, with the trade-off of higher rebubbling rates and possibly other postoperative complications. Studies with longer follow-up are needed to ascertain these differences between procedures.

Keywords

Descemet, descemet membrane endothelial keratoplasty, ultrathin, descemet stripping automated endothelial keratoplasty, systematic review

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Introduction

Descemet's membrane endothelial keratoplasty (DMEK) has gradually become the gold standard technique for the treatment of corneal endothelial failure, having now matched "traditional" Descemet stripping (automated) endothelial keratoplasty (DSEK/DSAEK) as the most widely performed keratoplasty techniques in the United States.[1] The reasons underlying this trend include the superior profile of DMEK compared with traditional DSEK/DSAEK in terms of visual outcomes, refractive results, and safety.[2–6] Although DMEK has a higher graft detachment (GD) rate,[2,3] most GDs are partial and self-limited, rebubbling rates decrease with surgeon experience, and the implications of rebubbling in graft survival are

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controversial.[7,8] Some corneal surgeons advocate that DMEK may be more technically challenging than DSEK/DSAEK, especially in complex eyes; this is currently disputed.[9]

Ultrathin DSAEK (UT-DSAEK), using refined graft preparation techniques to achieve lenticules with graft thickness (GT) below 130 μm,[10] and its recent variations which produce progressively thinner grafts (microthin DSAEK (MT-DSAEK) and nanothin DSAEK (NT-DSAEK),[11] have shown better visual outcomes and lower rejection rates compared with traditional DSAEK.[11] Until recently, there was limited evidence as to whether DMEK is superior to UT-DSAEK, which could be important from clinical and economical/political decision-making standpoints. However, increasing interest has arisen in the topic, and in a short period of time several systematic reviews (SRs) have emerged.

The aim of this paper is to provide a quality appraisal of the SRs comparing the outcomes of UT-DSAEK and its variations versus DMEK, as well as a synthesis of their evidence.

Methods/literature search

Eligibility criteria and search strategy

We conducted a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We performed a review of all SRs comparing outcomes of ultra-thin DSAEK (and its variant designations NT-DSAEK or MT-DSAEK) versus DMEK for corneal endothelial failure using three electronic databases (MEDLINE, Cochrane Database of Systematic Reviews, Google Scholar), in addition to a manual search of references in main articles up to 24th March 2023. We used search terms by title and abstract using variations of the terms ultra-thin DSAEK / UT-DSAEK / NT-DSAEK / nanothin DSAEK / microthin DSAEK / MT-DSAEK and Descemet membrane endothelial keratoplasty / DMEK. No restrictions by journal, year of publication and language were applied in the literature search.

Population

Patients with corneal endothelial failure who underwent endothelial keratoplasty.

Intervention

UT-DSAEK and its variations.

Comparator

DMEK.

Outcomes

All outcomes analyzed were eligible, including BCVA, residual spherical equivalent refractive error (SphEq), rebubbling rates, primary graft failure and secondary graft failure rates, immune rejection rates, endothelial cell density (ECD), central corneal thickness (CCT), and adverse events including postoperative elevated intraocular pressure (IOP).

Study design

Inclusion. SRs were included if they specified search strategy in at least two literature databases and included primary research; no restrictions were placed on the study design of the primary studies.

Exclusion. We excluded SRs without clearly defined research questions, search strategy or defined process of article selection. We also excluded articles other than SRs comparing UT-DSAEK vs DMEK, and we excluded articles retrieved in the literature search that were not written in English language.

Selection

We created a database of the search results of each database into a Microsoft Excel® sheet and eliminated duplicate results. Two researchers (NM-C, RP-V) independently screened the retrieved titles and abstracts, and the full-text articles of those classified as potentially eligible by either reviewer were independently analyzed by both reviewers. Where a consensus could not be reached by both reviewers, the senior author (JLG) reviewed disagreements.

Data extraction

We collected data including study authors, journal and year of publication patient baseline characteristics and differences, intervention and comparator, outcome measures, duration of follow-up, effect estimates – mean differences (MD) and odds ratios (OR) or risk ratios (RR) with confidence intervals as available –, and study design. One researcher (NM-C) completed data extraction, and a second researcher cross-checked (JPC).

Quality assessment and risk of bias

Two researchers (NM-C, AR) used the ROBIS tool for quality assessment and risk of bias analysis. Where a consensus could not be reached by both reviewers, the senior author (JLG) reviewed disagreements.

Data synthesis

Each outcome was narratively synthesized, including number of SRs using each outcome and effect estimates with confidence intervals (95%CI) from the source review. All outcomes that were reported in the SRs were included in our work, to avoid reporting bias.

Results

Database search identified 90 records, resulting in 71 studies after de-duplication (Supplemental Table 1). Four full-text articles were retrieved and analyzed after the initial screening of titles and abstract, and all four SRs were eligible for inclusion.[12–15] The PRISMA study flow diagram is presented in Supplemental Figure 1.

Review characteristics

Four SRs and meta-analyses met the inclusion criteria. The summary of reviews is presented in Table 1. All SRs included the randomized controlled trial (RCT) by Dunker et al.;[16] all SRs included the *Descemet Endothelial Thickness Comparison Trial* (DETECT) RCT, but while Maier et al.,[12] Dimtsas et al.[13] and Singh et al.[14] included the publication by Chamberlain et al.,[17] Hurley et al.[15] included the publication by Rose-Nussbaumer et al.[18] which analyzed the 2-year results in the same cohort. Three SRs[12,13,15] included the RCT by Matsou et al. which compared "MT-DSAEK" (all grafts had GT $\leq$ 130 µm, although a high proportion had a GT below 100-µm) to DMEK[19]; and only one SR[12] included the RCT by Kurji et al. comparing "NT-DSAEK" (with GT $\leq$ 50 µm) to DMEK.[20] All SRs included the retrospective fellow-eye study of Mencucci et al.,[21] and all SRs included the retrospective study by Romano et al.;[22] three SRs[12,14,15] included the fellow-eye study by Torras-Sanvicens et al.;[23] two SRs[14,15] included the retrospective study by Tourabaly et al. where DMEK was compared with DSAEK grafts of different GT and also compared with NT-DSAEK[24]; and one SR[13] included the retrospective study by Machalińska et al.[25]

Quality assessment and risk of bias

Risk of bias was assessed using the ROBIS tool, a validated tool designed specifically to assess the risk of bias in systematic reviews.[26] No SRs included in this study were considered at a "High risk of bias" (Table 2). All studies provided adequate analysis of risk of bias for the studies included. However, the SR by Singh et al. raised concerns for potential bias and was rated as "Unclear risk of bias" (Table 2). The remaining three SRs were considered as having a "Low risk of bias", although some concerns for potential bias were raised mainly related to the synthesis of findings.

Outcome evaluation. All SRs undertook a narrative synthesis and included meta-analyses for the outcomes.[12–15] All SRs evaluated postoperative BCVA.[12–15] Other outcomes included rebubbling rate (three studies),[12,13,15] ECD (four studies),[12–15] CCT (one study),[13] SphEq (one study),[13] rejection rate (one study),[12] graft survival (one study),[12] postoperative elevation of IOP (two studies),[12,13] and overall complications three studies).[13–15] Dimtsas et al. considered DMEK as the "intervention" and the UT-DSAEK as the "comparator",[13] whereas Maier et al., Singh et al. and Hurley et al. considered UT-DSAEK the "intervention" and DMEK the "comparator".[12,14,15]

Visual outcomes

The SRs by Maier et al.,[12] Dimtsas et al.[13] and Hurley et al.[15] included a meta-analysis of visual outcomes at different time points, focusing particularly on 12-month follow-up. Singh et al. performed a meta-analysis of postoperative BCVA, but time points analyzed in the studies included were variable from 12 to 32 months.[14] There were differences in the studies included in each SR, and as such there were variations in the pooled estimates for this outcome (Table 3). The largest difference in BCVA was reported by Maier et al., who observed a pooled MD of 0.50 (95%CI = 0.27–0.74, $p < 0.0001$) in BCVA 12-month follow-up.[12] This was different than the pooled MD estimates from the other three studies, who observed pooled MD of 0.06–0.07 in BCVA.[13–15] Dimtsas et al. also performed a meta-analysis of the 12-month SphEq and found a pooled estimate favoring DMEK over UT-DSAEK (MD = −0.12, 95%CI = −0.42–0.00, $p =$ 0.049); however, heterogeneity analysis for this outcome was not presented by the authors.[13] The study by Singh et al. observed high heterogeneity in their BCVA meta-analysis, which the authors considered to be likely due to the differences in postoperative time points analyzed in the studies included.[14] The SR by Hurley et al. concluded that the level of quality of evidence for the BCVA analysis was "High" using the GRADE system.[15]

Rebubbling

Only the studies by Maier et al., Dimtsas et al. and Hurley et al. performed a meta-analysis of the rebubbling rates.[12,13,15] There were differences in the studies included in each SR, and as such there were variations in the pooled estimates for this outcome (Table 4).The largest difference in rebubbling rate was reported by Dimtsas et al., who observed a 2.37-fold increase in risk of rebubbling defined by a fixed effects model after DMEK compared with UT-DSAEK.[13] In the other two SRs comparing

Table 1. Summary of systematic review of systematic reviews comparing ultrathin Descemet stripping automated endothelial keratoplasty (UT-DSAEK) to Descemet's membrane endothelial keratoplasty (DMEK).

Review and Year	Aim (participants)	Intervention / Comparator	Search strategy	No. of studies included	Studies included	Total no. of participants		F-U time after intervention (months)	Risk of bias assessment	Outcomes analyzed	Comments
						UT-DSAEK	DMEK				
Maier et al. (2023)[12]	Patients with FED and BK	UT-DSAEK / DMEK	MEDLINE, EMBASE, CDSR, LILACS	7 studies (3 RCT | 1 prospective study | 1 retrospective study | 2 retrospective fellow-eye studies)	Dunker et al. (2020) | Chamberlain et al. - DETECT (2019) | Matsou et al. (2021) | Kurji et al. (2018) | Torras-Sanvicens et al. (2021) | Mencucci et al. (2020) | Romano et al. (2020)	165	163	12	Clear quality appraisal of the studies	Primary outcome: BCVA | Secondary outcomes: ECD, rebubbling, rejection, graft failure, postoperative IOP elevation	
Dimtsas et al. (2023)[13]	Patients with FED and PBK	DMEK / UT-DSAEK	MEDLINE, CDSR	6 studies (4 RCT | 1 retrospective study | 1 retrospective fellow-eye study)	Chamberlain et al. DETECT (2019) | Dunker et al. (2020) | Matsou et al. (2021) | Machalinska et al. (2021) | Mencucci et al. (2020) | Romano et al. (2020)	151	149	12	Clear quality appraisal of the studies	BSCVA, ECD, Spherical equivalent, rebubbling, adverse events	Intervention DMEK, comparator UT-DSAEK
Singh et al. (2023)[14]	Patients with corneal endothelial failure	UT-DSAEK / DMEK	MEDLINE, EMBASE, SCOPUS	6 studies (2 RCT | 2 retrospective studies | 1 retrospective fellow-eye study | 1 cross-sectional comparative case series)	Chamberlain et al. DETECT (2019) | Dunker et al. (2020) | Mencucci et al. (2020) | Tourabaly et al. (2019) | Romano et al. (2020) | Torras-Sanvicens et al. (2021)	151	135	Unclear*	Good quality appraisal of the studies, but primary research method raises concern for potential bias (See ROBIS tool)	Primary outcome: BCVA | Secondary outcomes: ECD, complications	* A specific time point for analysis was not defined by the authors
Hurley et al. (2023)[15]	Patients with corneal endothelial failure	UT-DSAEK / DMEK	MEDLINE, EMBASE, CDSR	7 studies (3 RCT | 2 retrospective studies | 2 retrospective fellow-eye studies)	Rose-Nussbaumer et al. DETECT (2021) | Dunker et al. (2020) | Matsou et al. (2021) | Mencucci et al. (2020) | Romano et al. (2020) | Torras-Sanvicens et al. (2021) | Tourabaly et al. (2019)	189	173	12	Clear quality appraisal of the studies	BCVA, ECD, rebubbling, complications	

Legend: UT-DSAEK: ultrathin Descemet stripping automated endothelial keratoplasty; DMEK: Descemet's membrane endothelial keratoplasty; FED: Fuchs' endothelial dystrophy; BK: bullous keratopathy; MEDLINE: Medical Literature Analysis and Retrieval System Online; EMBASE: Excerpta Medica Database; CDSR: Cochrane Database of Systematic Reviews; LILACS: Latin American & Caribbean Health Sciences Literature; RCT: randomized controlled trial; BCVA: Best-corrected visual acuity; ECD: endothelial cell density; IOP: intraocular pressure; PBK: pseudophakic bullous keratopathy; BSCVA: best spectacle-corrected visual acuity.

Table 2. ROBIS tool assessment of risk of bias in the reviews included in this overview of systematic reviews.

Studies	Study eligibility criteria	Identification and selection of studies	Data collection and study appraisal	Synthesis and findings	Risk of bias in the review	Rationale for concern		
Maier et al.	LOW	LOW	LOW	LOW	LOW	-	-	-
Dimtsas et al.	LOW	LOW	LOW	LOW (*)	LOW	(*) Analyzing overall postoperative complications without including rebubbling would have provided more relevant findings.	No forest plot and heterogeneity analysis were made for some of the outcomes analyzed (CCT, postoperative elevated IOP).	-
Singh et al.	LOW	UNCLEAR*	LOW	UNCLEAR (*) **	UNCLEAR	* The primary search was limited by year, language, and country of publication, which may raise potential bias.	** Some inconsistency between manuscript body and forest plot results; unclear conclusions regarding ECD; significant heterogeneity in BCVA outcome analysis	(*) Analyzing overall postoperative complications without including rebubbling would have provided more relevant findings.
Hurley et al.	LOW	LOW	LOW	LOW (*)	LOW	(*) Analyzing overall postoperative complications without including rebubbling would have provided more relevant findings.	-	-

Legend: CCT: central corneal thickness; IOP: intraocular pressure; ECD: endothelial cell count; BCVA: best-corrected visual acuity.

Table 3. Visual outcome analysis of ultrathin DSAEK versus DMEK.

	No. studies	Total no. of participants		Time point analysis of BCVA	MD	95% CI of MD	p-value	Heterogeneity (I-square)	Conclusion	Comments
		UT-DSAEK	DMEK							
Maier et al. (2023)	7	154	152	12 months	0.50	0.27–0.74	$p <$ 0.0001	9%%	In favour of DMEK	-
Dimtsas et al. (2023) **	5	127	121	12 months	−0.075	−0.12 - −0.03	$p =$ 0.001	49%	In favour of DMEK	12-month analysis SphEq favouring DMEK MD -0.12 (95%CI -0.42 - 0.00) ($p = 0.049$)
Singh et al. (2023)	4	120	110	12–32 months	0.06	0.04–0.09	$p <$ 0.0001	52% (*)	In favour of DMEK	(*) Significant heterogeneity
Hurley et al. (2023)	7	189	173	12 months	0.07	0.04–0.10	$p <$ 0.001	32%	In favour of DMEK	GRADE Quality of Evidence: High

Legend: UT-DSAEK: ultrathin Descemet stripping automated endothelial keratoplasty; DMEK: Descemet's membrane endothelial keratoplasty; BCVA: best-corrected visual acuity; MD: mean difference; CI: confidence interval; SphEq: spherical equivalent.
**Intervention DMEK, comparator UT-DSAEK.

Table 4. Rebubbling rate comparison between ultrathin DSAEK and DMEK.

Review and Year	No. studies	Total no. of participants		RR	95% CI of RR	p-value	Heterogeneity (I-square)	Conclusion
		UT-DSAEK	DMEK					
Maier et al. (2023)	6	154	153	0.33	0.16–0.67	$p =$ 0.0025	0%	Rebubbling rate is lower after UT-DSAEK compared with DMEK
Dimtsas et al. (2023) **	6	151	149	2.37	1.25–4.49	$p = 0.008$	0%	Rebubbling rate is 2.37 times higher after DMEK compared with UT-DSAEK
Hurley et al. (2023)	5	119	117	0.40	0.22–0.73	$p = 0.003$	0%	Rebubbling rate is lower after UT-DSAEK compared with DMEK (GRADE Quality of Evidence: High)

Legend: UT-DSAEK: ultrathin Descemet stripping automated endothelial keratoplasty; DMEK: Descemet's membrane endothelial keratoplasty; RR: risk ratio; CI: confidence interval.
**Intervention DMEK, comparator UT-DSAEK

Table 5. Postoperative complications comparison between ultrathin DSAEK and DMEK.

Review and Year	Type of AE	No. studies	Total no. of participants		Time point analysis of AEs	RR	95% CI of RR	p-value	Heterogeneity (I-square)	Conclusion	Comments
			UT-DSAEK	DMEK							
Maier et al. (2023)	Graft failure	6	133	138	Unclear	0.65	0.18–2.30	$p=0.50$	0%	No significant differences in graft failure risk between procedures	Graft failure 2 UT-DSAEK / 5 DMEK
	Graft rejection	5	123	128	Unclear	1.40	0.27–7.30	$p=0.69$	0%	No significant differences in graft rejection rates between procedures	Graft rejection 1 UT-DSAEK / 0 DMEK
	Postoperative elevated IOP	4	95	100	Unclear	1.14	0.60–2.18	$p=0.69$	0%	No significant differences in postoperative elevated IOP rate between procedures	-
Dimtsas et al. (2023) **	Overall (including donor preparation failure, rebubbling, retransplantation, rejection, postoperative elevated IOP)	6	151	149	Unspecified	1.49	1.02–4.49	$p=0.039$	0%	DMEK group had 1.48 times greater risk for AEs; with comparable postoperative elevated IOP rate	Retransplantation 3 DMEK / 0 UT-DSAEK; Rejection 1 DMEK / 0 UT-DSAEK
	Postoperative elevated IOP	6	151	149	Unspecified	0.91	0.45–1.78	$p=0.790$	N/R		
Singh et al. (2023)	Overall (including graft displacement, rebubbling, graft rejection, graft failure, postoperative elevated IOP)	3	68	72	12 months	0.27	0.12–0.59	$p=0.001$	0%	Lower complication rate in UT-DSAEK	Complications 21 UT-DSAEK / 48 DMEK
Hurley et al. (2023)	Overall (including donor preparation failure, rebubbling, postoperative elevated IOP, graft failure, graft rejection, retransplantation, posterior synechiae, retinal tears and cystoid macular edema)	5	119	117	Unclear	0.57	0.36–0.90	$p=0.02$	39%	Lower complication rate in UT-DSAEK	Complications 33 UT-DSAEK / 59 DMEK; (GRADE Quality of Evidence: Moderate)

Legend: UT-DSAEK: ultrathin Descemet stripping automated endothelial keratoplasty; DMEK: Descemet's membrane endothelial keratoplasty; AE: adverse event; RR: risk ratio; CI: confidence interval; IOP: intraocular pressure.

**Intervention DMEK, comparator UT-DSAEK.

rebubbling rates, UT-DSAEK was associated with a 60–67% lower risk of rebubbling (RR = 0.33 to 0.40).[12,15] Hurley et al. concluded that the quality of evidence for the rebubbling analysis was "High" using the GRADE system.[15]

Other postoperative complications

The studies by Dimtsas et al., Singh et al. and Hurley et al. performed meta-analyses to compare DMEK and UT-DSAK in "overall complications" (Table 5).[13–15] The largest difference in complication rate was reported by Singh et al., who observed that patients undergoing UT-DSAEK had 73% less risk of postoperative complications compared with patients undergoing DMEK (OR = 0.27, 95%CI = 0.12–0.59, $p = 0.001$).[14] Hurley et al. concluded that UT-DSAEK was associated with 43% less risk of complications compared with DMEK (RR = 0.57, 95%CI = 0.36–0.90, $p = 0.02$),[15] and Dimtsas et al. reported a 1.49-fold increased risk of complications after DMEK (RR = 1.49, 95%CI = 1.02–4.49, $p = 0.039$).[13] The analysis of "overall complications" raises concern for potential interpretation bias, since a large proportion of complications in all studies were rebubblings. This means that other individual postoperative complications may not conform to the findings of their meta-analyses. For instance, Dimtsas et al. also performed a meta-analysis of postoperative elevation of IOP, and found no significant differences between DMEK and UT-DSAEK (RR = 0.91, 95%CI = 0.45–1.78, $p = 0.790$),[13] comparable with the findings of Maier et al. (RR = 1.14, 95%CI = 0.60–2.18, $p = 0.69$).[12] Only the study by Maier et al. analyzed the rejection rates and graft failure as standalone parameters, and found no significant differences between both procedures (graft failure RR = 0.65, 95%CI = 0.18–2.30, $p = 0.50$ | graft rejection RR = 1.40, 95%CI 0.27–7.30, $p = 0.69$).[12] Hurley et al. found that the GRADE level of quality of evidence for the comparison of "overall complications" between UT-DSAEK and DMEK was "Moderate".[15]

Endothelial cell density

All SRs included in this overview included a meta-analysis of the ECD at 12-month postoperative follow-up.[12–15] There were differences in the studies included in each SR, and as such there were variations in the pooled estimates for this outcome (Supplemental Table 2). Maier et al. found that pooled estimates could not be interpreted for ECD due to significant heterogeneity,[12] and the other SRs similarly found significant heterogeneity for this analysis.[13–15] The SR by Dimtsas et al. also included a meta-analysis of the 12-month CCT, and found a pooled estimate in favor of DMEK (MD = −47.1, 95% CI = −62.0–32.0, $p < 0.001$)[13]; however, this analysis raises concern for potential interpretation bias, since heterogeneity was not reported, and particularly since this difference may be at least partly explained by the differences in donor lenticule graft thickness between DMEK and UT-DSAEK.[13] The meta-analysis for ECD by Singh et al. has some inconsistencies which raise concern for potential bias (Supplemental Table 2).[14]

Conclusions

This is the first systematic review of SRs specifically addressing the outcomes of corneal endothelial grafting. The relevance of this type of overviews of SRs is highlighted by the findings that only 28–70% of SRs in ophthalmology are considered reliable.[27–30] This is in line with our findings that 25% of the SRs analyzed had an unclear risk of bias after applying the ROBIS tool, that 50% raised potential concerns due to heterogeneity and inconsistent reporting of data, and that three SRs compared "overall complications" rather than reporting each complication individually. Given the weight that rebubbling has in the complication rates after DMEK, at least this outcome should not have been included among other less frequent complications. Besides, the rejection and graft failure rates ought to have been analyzed independently, since these are important outcomes to analyze when two techniques of corneal transplantation are compared.

This summary of SRs provides the highest level of evidence that DMEK leads to higher levels of BCVA in comparison with UT-DSAEK and its variations. The favorable visual outcomes after DMEK are likely due to the lack of posterior stromal tissue in the donor graft, which also leads to lower levels of posterior corneal HOAs compared with UT-DSAEK.[25,31] However, it is unclear whether differences BCVA after 1 year of follow-up are relevant, since the study with the longest follow-up after UT-DSAEK observed a mean BCVA of 0.09 logMAR and that 53.4% of eyes achieved BCVA > 20/20 Snellen,[32] which is comparable with the results of long-term series of DMEK surgery.[5,6]

Rebubbling rates after UT-DSAEK are lower than those after DMEK. However, as previously stated, the implications for rebubbling on graft survival are unclear.[7,8,33] ECD after UT-DSAEK and DMEK were comparable, although significant heterogeneity was observed by all SRs. Endothelial cell loss after DMEK and UT-DSAEK is likely comparable, and this is also true when comparing the endothelial cell loss after conventional DSEK/DSAEK. Although no comparative studies are available for follow-up longer than 1 year, reported 5-year endothelial cell loss rates after UT-DSAEK are also comparable with those of DMEK and those of DSEK/DSAEK.[5,33–36]

Importantly, this systematic review of SRs found that immune rejection rates and other postoperative complications after UT-DSAEK may be comparable with those

after DMEK during the first postoperative year. However, we consider that this is a short follow-up period to establish definite conclusions regarding rejection risk. Although most rejection episodes occur during the first two years after EK,[37] the cumulative rejection risk increases with time after endothelial keratoplasty, and studies with longer follow-ups have reported up to 7% rejection rates at 5 years in UT-DSAEK,[32] compared with 2.5–4% rejection rates at 5 to 10 years after DMEK.[5,6,37]

The main strength of our overview is that we identified the relevant differences and contrasts between the SRs. The main limitation of our systematic review of SRs is that we used few electronic databases, although relevant ones. One important limitation of current SRs of UT-DSAEK versus DMEK is that no review compared the cost-effectiveness of the two techniques, which should be relevant for decision makers. DMEK showed to be cost-effective in comparison to conventional DSAEK in the United States,[38] but a recent multicenter RCT conducted in the Netherlands found that UT-DSAEK was cost-effective compared with DMEK, as DMEK had higher costs (mainly caused by higher rebubbling and regraft rates) while quality-adjusted life years were lower.[39]

In conclusion, there is an overall good quality of evidence on the comparison of outcomes between DMEK and UT-DSAEK and its variations, although a quarter of SRs had an unclear risk of bias, and potential concerns for heterogeneity and inconsistency in reporting of data were found in this overview of SRs. DMEK eyes may expect to reach higher levels of BCVA compared with eyes undergoing UT-DSAEK and its variations, with the trade-off of a higher rebubbling rate. It is unclear whether the rate of other postoperative complications is comparable between the two techniques (apart from rebubbling). Comparative studies with longer follow-up are crucial to elucidate the differences in BCVA, as well as in cumulative rejection rates and graft failure after the first year postoperatively.

Authorship

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Supplemental material

Supplemental material for this article is available online.

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Publication IX

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REVIEW ARTICLE

Rho kinase inhibitors—a review on the physiology and clinical use in Ophthalmology

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Abstract
The Rho kinase (ROCK) signaling pathway is involved in several cellular events that include cell proliferation and cytoskeleton modulation leading to cell adhesion. The ROCK pathway in the human eye has been hypothesized to play important roles in corneal endothelial cell physiology and pathologic states. In addition, ROCK signaling has been identified as an important regulator of trabecular meshwork (TM) outflow, which is altered in glaucomatous eyes. These roles in corneal and glaucomatous disease states have led to the growing interest in the development of drugs selectively targeting this pathway (ROCK inhibitors). The authors provide a review of the literature on the pathobiology of the ROCK signaling in corneal endothelial disease, glaucoma, and vitreoretinal disease, as well as the clinical usefulness of ROCK inhibitors in Ophthalmology.

Keywords Rho kinase · Rho kinase inhibitors · Corneal endothelial disease · Glaucoma · Vitreoretinal disease

Introduction

Since the introduction of protein kinase inhibitors (PKI) and their approval by the US Food and Drug Administration (FDA) for the treatment of neoplastic diseases, there has been an increasing interest in basic, translational, and clinical research to produce novel PKI drugs, some of which have been approved by the FDA. In Ophthalmology, a particular class of PKI, Rho kinase inhibitors (RKIs), has grown great clinical interest, due to the further understanding of their role in normal ocular physiology and eye disease states such as glaucoma and corneal endothelial disease.

Rho kinase and ROCK signaling pathways

The Rho proteins belong to the GTPase family of small, monomeric molecules which are molecular switches that control several complex cellular processes through a wide variety of signal transduction pathways [1]. Rho is activated in a highly regulated fashion by the binding of guanine triphosphate (GTP), causing its interaction with one of over 60 effector proteins; of these, Rho kinases (ROCKs) are among the most extensively characterized [2]. In humans, two isoforms of ROCK have been described: ROCK-I (ROKβ) and ROCK-II (ROKα) [1]. Both are serine/threonine molecules with a small molecular weight (160 kDa), containing an N-terminal kinase domain, and share similar amino acid identities, as well as an identical ATP-binding pocket; in addition, these isoforms share several downstream substrates, suggesting some redundancy in their biological roles [2, 3]. Activation of GTP-bound Rho protein leads to activation of ROCK, which in turn leads to downstream phosphorylation of a variety of substrates promoting many cellular functions, including modulation of

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the actin skeleton, smooth cell contraction, cell migration, regulation of cell polarity, gene transcription, cell cycle progression and cell proliferation, microtubule dynamics, vesicular transport pathways, and a number of enzymatic activities [3].

ROCK molecules are ubiquitously expressed in all cell tissues and organs, although the degree of expression may vary according to cell tissue. ROCK molecules and the ROCK pathway have been implicated in a variety of disease processes, including vascular, neurologic, kidney, and neoplastic diseases. Their role in cell proliferation, cell migration, and cellular contraction has made them potential therapeutic targets. Over the past two decades, a number of inhibitor molecules have been developed, with different relative potencies and biological functions.

Rho-associated kinase signaling in ocular physiology and disease

Cornea

Corneal physiology

Rho/ROCK signaling has been shown to regulate a number of functions in all corneal layers, including cell proliferation, epithelial differentiation, modulation of cell migration, and cell adhesion.

Limbal to corneal epithelial transition has been associated with increased expression of ROCK-I, and in vitro studies of cultured animal corneal epithelial cells have indicated that ROCK-I expression is regulated during the progression of the cell cycle at the G1 and G1/S progression stages [4].

ROCK signaling is also involved in the mechanisms of corneal wound healing. There is increased expression and activation of both ROCK isoforms in in vitro human corneal epithelial cells and in vivo animal studies [5]. In addition, corneal stromal keratocytes differentiate to fibroblasts and myofibroblasts during wound healing. This differentiation process is accompanied by the expression of α-smooth muscle actin and the assembly of a stress fiber network and large focal adhesions, which lead to increased contractility; these changes have been shown to be regulated by the ROCK pathway [6, 7].

Corneal endothelial cells (CECs) are responsible for maintaining corneal transparency both for its barrier and pump functions. These cells have very limited, if any, regenerative capability in in vivo human corneas, and endothelial cell counts (ECCs) drop in a continuous fashion with age after the third decade, at an approximate rate of 0.6% loss per year [8]. In corneal endothelial disease states, such as Fuchs' endothelial corneal dystrophy (FECD) or post-operative corneal endothelial decompensation, increased CEC loss is initially compensated by migration and spreading of the remaining CECs, which undergo endothelial-to-mesenchymal transition with acquisition of fibroblast-like contractile properties. This compensatory mechanism helps to keep the corneal transparency until the functional reserve of the corneal endothelium is overcome at approximately 500 cells/mm^2. At this point, the remaining CECs are no longer able to maintain transparent cornea, and corneal haze and vision loss ensue.

There is evidence of expression of RhoA, ROCK-1, and ROCK-2 in human CECs [9], but the greatest body of evidence for the implication of ROCK signaling pathways in CEC survival, migration, and contraction comes from studies using RKIs. Inhibition of ROCK signaling with specific RKIs appears to increase CEC proliferation in vitro and in in vivo animal models of corneal endothelial injury, enhancing the rate of wound healing and recovery of corneal transparency [9–14]. Rabbit CECs have shown greatest proliferative capacities than non-human primate CECs; interestingly, dogs may be an alternative model of corneal endothelial disease, as dog CECs have shown similar proliferative capacity than non-human primates [15]. RKI molecules (Y-27632 and H-1152) have shown to reversibly change the cytoskeleton by the loss of actin stress fibers, focal cell adhesions, and cell-cell tight junctions, thus promoting proliferation and migration of CEC [9, 16]. Studies of in vitro cultured human CECs treated with RKIs showed inhibition of the endothelium-mesenchymal transition, increased ECC, decreased pleomorphism and polymegethism, increased expression of zonula occludens adhesion molecules, and increased expression of the Na+/K+-ATPase ionic pump [17, 18].

RKIs in corneal endothelial diseases

Based on animal and in vitro human CEC studies, increasing clinical research is emerging regarding the potential benefits of RKI treatment in corneal endothelial diseases, given their potential to promote CEC proliferation by modulation of cyclin and p27 (regulators of the G1/S transition of the cell cycle), CEC regeneration [19, 20].

Small case series of patients with FECD or iatrogenic bullous keratopathy who underwent diseased endothelium removal by transcorneal freezing followed by topical treatment with Y-27632 eye drops six times daily for 1 week showed improved corneal clarity and even corneal clearing, as well as reduced corneal edema as measured by corneal pachymetry, improved ECC, and improved visual acuity. Reported outcomes appear to be long-standing, with maintained results after 2 years of treatment [21, 22].

Clinical evidence has suggested that patients with FECD may be successfully treated with central descemetorrhexis without endothelial keratoplasty (DWEK), although this remains controversial. In a small prospective, interventional case series of DWEK for FECD, a small subset of patients required salvage therapy with topical RKI (Y-27632 or

ripasudil). In this study, the authors found topical ripasudil to be a potentially useful salvage agent in failed DWEK cases, expanding the possible applications of DWEK surgery [23].

Tissue engineering is an expanding field in Medicine, and its potential in Ophthalmology for the treatment of corneal disease is being actively explored, including the transplantation of cultivated corneal limbal stem cells in severe limbal stem cell deficiency states. Two strategies have shown promising results in corneal tissue engineering, transplantation of bioengineered CEC sheet, and direct injection of cultivated CEC suspension in the anterior chamber. Bioengineered CEC sheets on a collagen substrate yield a fragile monolayer of CEC which make tissue manipulation in the anterior chamber technically challenging [19]. Direct injection of CEC in the anterior chamber seems easier, safer, and less invasive than the former technique. In addition, increasing promise derived from studies in animal models of corneal endothelial decompensation in human in vitro showing RKI (Y-27632) improves CEC adhesion onto the Descemet's membrane and improves corneal clearing [19]. The first clinical trial of cell-based therapy to treat corneal endothelial dysfunction has recently been published. Eleven patients with bullous keratopathy underwent intracameral injection of cultured human CECs in combination with a RKI (Y-27632). Primary outcome measured was restoration of corneal transparency with an ECC > 500 cell/mm^2 at 24 weeks post-treatment; secondary outcomes were corneal thickness < 630 μm, and improvement in visual acuity of two lines or more at 24 weeks. At 24 weeks after CEC plus ROCK injection, all treated eyes met the primary outcome, with ECC of over 950 cells/mm^2 in all cases. Ten eyes achieved a corneal thickness of less than 630 μm, and nine eyes showed improvement in visual acuity of two lines or more. Long-term outcomes also appeared to be favorable, with reduced corneal thickness in all treated eyes and significantly improved visual acuity maintained at 2-year follow-up [24].

Evidence for the potential role of RKIs in corneal endothelial disease is presented in Table 1. The information about RKIs already studied in patients with corneal endothelial disease is presented in Table 2.

Glaucoma

Aqueous humor dynamics and IOP modulation

The trabecular meshwork (TM) is a complex tissue consisting of trabeculocytes, extracellular matrix (ECM), and empty spaces. Its juxtacanalicular tissue (JCT) portion is the site of greatest resistance to aqueous humor (AH) outflow, a mechanism that has been implicated in the pathogenesis of primary open-angle glaucoma (POAG) [104]. Besides the "anatomic" configuration of the TM, its functional properties also contribute in the dynamics of AH outflow. The TM shows smooth muscle-like properties, due to expression of smooth muscle actin and myosin and ion channels. These contractile properties are modulated by numerous molecules, including contractile agonists, cytokines, and growth factors [26]. The relaxation of the TM results in increased intercellular spaces and increased aqueous outflow.

Rho and ROCK signaling pathways have been implicated in the dynamics of aqueous humor (AH) outflow pathways. These molecules are expressed in the trabecular meshwork (TM) and have been shown to lead to smooth muscle sensitization in a calcium-independent manner, leading to contraction of the TM via phosphorylation of myosin light chain and LIMK/cofilin pathways which lead to formation of stress fibers and focal adhesion complexes in TM cells, which lead to increased conventional outflow resistance. RKIs exert effects on the cytoskeleton of the TM cells and Schlemm's canal cells, decreasing the density of actin stress fibers [25, 27, 28, 40], which leads to changes in TM cell morphology and changes in the permeability of Schlemm's canal endothelial cells [41, 55]; these effects vary according to the relative potency of each RKI, which has been studied in vitro [87]. In addition, ROCK signaling leads to oxidative stress in the TM, and RKIs have shown to suppress this mechanism by increasing expression of catalase and reducing production of reactive oxygen species [29].

Retinal ganglion cell and optic nerve head

Rho and ROCK are highly expressed in the central nervous system (CNS), optic nerve, and retinal ganglion cells (RGCs). Evidence for the role of this signaling pathway has been mostly revealed from pharmacological studies using RKIs [33]. Rho/ROCK signaling may be involved in the neural retinal degenerative changes following traumatic optic neuropathy and glaucomatous optic neuropathy (GON), promoting cell migration, glial activation, and RGC apoptosis. Besides, Rho/ROCK pathway may inhibit neurite elongation in CNS axons in a number of disease states and in RGC axons following trauma [34, 35].

Retinal blood flow and vasomotor tone are also mediated by endothelin-1 (ET-1)-induced ROCK signaling, which promotes vasoconstriction [105]. Ocular blood flow may be improved by RKIs, as shown in normal and disease rabbit models and in normal rat models, which showed increased optic nerve head (ONH) blood flow after topical RKI administration in both, as measured by LASER speckle flowgraphy (LSFG) [32, 44, 106] and by micro-LSFG [30]. RKI induces relaxation of vascular smooth muscle cells, leading to dilation of ONH blood vessels. To date, no studies have formally assessed the effects of RKIs on ocular blood flow in human subjects. Interestingly, however, a recent pilot study of 13 eyes suggested that visual acuity improved in most patients with recent non-arteritic anterior ischemic optic neuropathy

Table 1 Rho-associated kinase signaling pathway in ocular disease: pathophysiology, proposed rationale for the use of Rho kinase inhibitors (RKIs), and experimental/clinical evidence of RKI in ocular disease

Disease	Proposed role of Rho/ROCK signaling pathway in the pathophysiology of disease	Proposed effects of Rho kinase inhibitors	Rho kinase inhibitors studied	Evidence	References
Primary corneal endothelial disease	• LIMK2/cofilin pathway, myosin light chain, and CPI-17 mediated [9]; formation and assembly of actomyosin stress fibers • Focal adhesions • Cell contraction • Increased production of ECM • Inhibition of CEC cell cycle progression and CEC apoptosis [11–13, 18, 20, 21]	• Induced CEC proliferation via PI3-kinase signaling-related upregulation of cyclin D and downregulation of p27 [15, 20] • Inhibition of CEC apoptosis [13] • Induction of CEC proliferation [11, 12] • Promotion of CEC engraftment by suppressing actomyosin contraction [18]	• Y-27632 [9, 10, 13, 16, 21, 22, 24] • Y-39983 [20]; H-1152 [9] • Ripasudil [23] • Of note, H-1152 may be more potent than Y-27632 in promoting CEC proliferation and migration [9].	In addition to in vitro and in vivo studies with animal models of corneal endothelial disease, clinical evidence has increasingly shown the clinical usefulness of topical RKI [21–23] and injection of RKI in the anterior chamber in the setting of corneal endothelial disease and transplantation [24]. Corneal clearing and visual improvement has been demonstrated in patients with Fuchs' endothelial corneal dystrophy following DWEK [23] and injection of CECs into the anterior chamber in combination with RKI [24]	See description in this table, and also Section 2.1—cornea in the text for references
Ocular hypertension (OHT) and primary open-angle glaucoma (POAG)	• Increased ECM production in the TM due to increased TGF-β • TM cell contraction by actomyosin changes in a calcium-independent manner mediated in part by endothelin-1 [25] • Increased outflow resistance due to TM cell contraction and overexpression of adhesion molecules in SCE cells 2 [26–28] • Oxidative stress due to increased ROS production [29] • Retinal and optic nerve head vasoconstriction and altered blood flow [30–32] • Prevention of microglial-mediated axonal elongation and retinal ganglion cell repair following injury leading to RGC death [33–35] • Increased TGF-β-induced cell contraction, cytoskeletal changes, focal cell adhesions, and delayed myofibroblast transdifferentiation leading to conjunctival scarring and trabeculectomy bleb failure [36–39]	• TM cell relaxation via calcium-independent pathway and disruption of actin bundles • Downregulation of TGF-β induced matrix deposition in the TM [25, 28, 40] • Disruption of ZO-1 adhesion molecules in SCE cells [41] • Norepinephrine transport inhibition (NET)-induced decrease in AH production (netarsudil) by reducing blood flow to ciliary processes [42] • NET-induced reduction of episcleral venous pressure [43] • Improved ocular blood flow in the ONH [31, 32, 44] • RGC survival and axonal regeneration [33, 35, 45] • Reduced post-trabeculectomy scarring by reducing subconjunctival collagen deposition and inhibition of myofibroblast transdifferentiation [36–38]	• Y-27632 [25, 28, 34, 37] • Y-39983 [34] • AMA0526 [38] • SB772077B [40] • Fasudil [32, 45] • Netarsudil [35] • Ripasudil [36, 41, 44, 45] • AR-12286 [47]	In addition to multiple in vitro and in vivo animal studies, there is a large body of evidence derived from large randomized clinical trials [46] and other clinical studies that show topical RKIs are effective in lowering IOP, and that their clinical usefulness is probably best as adjunctive therapy in combination with other topical ocular hypotensive drugs.	See description in this table, and also Section 2.2—glaucoma in the text for references

Table 1 (continued)

Disease	Proposed role of Rho/ROCK signaling pathway in the pathophysiology of disease	Proposed effects of Rho kinase inhibitors	Rho kinase inhibitors studied	Evidence	References
Pseudoexfoliation glaucoma (PXG)	• ROCK signaling causes TM outflow changes as in POAG • Exfoliation material deposition causes TM outflow obstruction [47] and inflammation [48]	Improve conventional trabecular outflow by modulation of TM extracellular matrix, TM cell behavior, and SCE cells [49]	• Ripasudil [48–50]	Clinical evidence has produced mixed results regarding whether the use of adjunctive treatment with topical RKIs provides additional IOP-lowering benefit in pseudoexfolation glaucoma [47, 49, 50].	Skaat et al. (2016), Sato et al. (2016), Matsumura et al. (2017), Komizo et al. (2018)
Pigment dispersion glaucoma (PDG)	• ROCK signaling causes outflow changes as in POAG • Pigment particles induce TM stress fibers, have TM antiphagocytic properties, and increase TM cell adhesions [51]	• Increased phagocytically active cells in the TM to remove pigment deposition • Disruption on actin stress fibers in the TM	RKI-1447 (dual ROCK-1/2 inhibitor) [51]	Porcine model of PDG showed that RKI increased outflow facility by 38.25% and reduced IOP by 33.58% [51]	Dang et al. (2018)
Uveitic glaucoma	• Induction of non-specific inflammation—oxidative stress, cyclooxygenase-2, NF-kB p65—and decrease in anti-inflammatory cytokines IL-17 and IL-21 [52] • Obstruction of the TM by inflammatory cells and protein • TM cell autolysis and phagocytosis by inflammatory cells • Increased blood-aqueous barrier (BAB) permeability related to increased expression of TNF-α and matrix metalloproteinases (MMP-1, MMP-2, and MMP-9) [53]	• Downregulation of pro-inflammatory molecules, oxidative stress, and matrix metalloproteinases [52, 53] • Reduction of anterior chamber cells and proteins with reduced TM obstruction • Alteration of non-pigment ciliary epithelial cell shape, which may promote reorganization of the BAB [53]	• Ripasudil [50, 52, 53] • Y-27632 [53, 54]	In addition to in vitro models of ocular inflammation, there is clinical evidence for the potential utility of topical RKI in uveitic glaucoma. However, the clinical results are conflicting regarding their additional IOP-lowering benefit as adjunctive therapy [50, 52, 53].	Yamada et al. (2017), Yasuda et al. (2017), Komizo et al. (2018)
Corticosteroid (CS)-induced glaucoma	• ROCK signaling causes outflow changes as in POAG • CS increase TM stiffness • CS increase TM and Schlemm's endothelial cells' tight junction molecules (ZO-1) [52], mechanisms which increase outflow resistance [55] • Dexamethasone induces RhoA activation and collagen production [27, 54]	• Disruption of actin bundles in TM cells • Disruption of ZO-1 expression in SCE cells [52, 55]	Ripasudil [50, 52]	Clinical evidence has produced mixed results regarding whether the use of adjunctive treatment with topical RKIs provides additional IOP-lowering benefit in corticosteroid-induced glaucoma [50, 52].	Yasuda et al. (2017), Komizo et al. (2018)
Diabetic retinopathy (DR)	• ROCK-1 induces retinal vasoconstriction via non-apoptotic endoluminal blebbing [56] and via ET-1 [57–59] • Endothelial cell activation [56]	• Relief of vasoconstriction [56] at least in part due to relieve of ET-1-mediated venular constriction [59]	• Y-27632 [63, 65, 70] • AMA0428 [67] • Ripasudil [69]	In addition to in vitro and in vivo studies with animal models of DR, there is already clinical evidence from 2 small case series of patients with refractory diabetic macular	Arita et al. (2008), Arita et al. (2010), Yokota et al. (2007), Oku et al. (2001), Yamaguchi et al. (2016), Rothschild et al. (2016), Khuu et al. (2017), Hollanders et al. (2016), Lu

Table 1 (continued)

Disease	Proposed role of Rho/ROCK signaling pathway in the pathophysiology of disease	Proposed effects of Rho kinase inhibitors	Rho kinase inhibitors studied	Evidence	References
	• Downregulation of eNOS [60] • Induced expression of PDGF-BB by retinal vessel pericytes [61] • Leukostasis and leukocyte adhesion to retinal vessel wall mediated by ICAM-1, leading to neutrophil-induced endothelial cell injury mediated by Fas [60, 62] • Increased production of VEGF [61] • Muller cell morphology changes and dysfunction and Muller cell apoptosis induced by hypoxia and oxidative stress [63, 64] • ROCK-1 signaling causes disruption of the outer blood-retinal barrier (BRB) by overactivation of RPE cells [56] • ROCK-1 signaling causes disruption of the inner BRB [60, 62] via downregulation of occludin molecules [65] • Endothelial cell migration [66] • Contraction of proliferative membrane [66] • Retinal neurodegeneration [67] via NMDA neuronal excitotoxicity [60] • Increased TFG-β-mediated membrane proliferation and contraction and myofibroblastic transdifferentiation leading to proliferative diabetic retinopathy [68]	• Inhibition of leukostasis and leukocyte adhesion to retinal vessels, with reduced neutrophil-induced endothelial cell damage [60, 67] • Restored eNOS activation and protection of retinal vascular endothelial cells [60] • Reduced Muller cell apoptosis and migration under oxidative stress [63, 64] • Reduced VEGF production [61] and reduced VEGF-induced endothelial cell migration and retinal neovessel formation [69] • Reduced retinal neurodegeneration [67, 70] • Reduced membrane formation and contraction [68]	• Fasudil [56, 60, 61, 64, 65, 68, 71, 72] • siRNA ROCK-1 [65]	edema in which combined intravitreal fasudil and anti-VEGF injections improved visual acuity and retinal thickness [71, 72].	et al. (2014), Zhang et al. (2018), Moshirfar et al. (2018), Chen et al. (2018), Amadieh et al. (2013), Nourinia et al. (2013), Kita et al. (2008)
Age-related macular degeneration (AMD)	• ROCK-2 isoform induces M2-like macrophage polarization [73, 74] which leads to increased inflammation and angiogenesis • ROCK increases VEGF and PlGF production [75] and promotes VEGF-induced endothelial cell migration and endothelial cell proliferation [75]	• Inhibition of endothelial cell proliferation and VEGF-induced endothelial cell migration [75] • Reduced inflammation [73, 75] and reduced M2-like macrophage polarization [73] • Blocked neovascularization and leakage [73, 75] • Reduced CNV membrane size [73] • Reduced fibrosis after CNV [75]	• Y-27632 [73, 76, 77] • Fasudil [73] • AMA0428 [75] • Selective ROCK-2 inhibitors [73, 76]	Mouse [73, 75] and monkey [73] with LASER-induced CNV (a model of CNV); human AMD-CNV or idiopathic CNV membranes in vitro [73]; hESC-RPE and iPSC-RPE cells in vitro [76, 77].	Zandi et al. (2015), Zanin-Zorov et al. (2016), Hollanders et al. (2015), Croze et al. (2014), Croze et al. (2016)

Table 1 (continued)

Disease	Proposed role of Rho/ROCK signaling pathway in the pathophysiology of disease	Proposed effects of Rho kinase inhibitors	Rho kinase inhibitors studied	Evidence	References
	• RhoA/ROCK and downstream molecules are overexpressed in choroidal neovascular membranes (NV-AMD) [73] • ROCK signaling leads to EMT which limits the therapeutic effect of hESC-RPE and iPSC-RPE cell transplantation for geographic atrophy (GA) [76, 77]	• Inhibition of the EMT switch in transplanted RPE cells [77], improved RPE cell proliferation with dual ROCK-1/2 inhibitor but not with selective ROCK-2 inhibitor [76], and improved RPE cell attachment in areas of geographic atrophy [76]			
Retinal detachment (RD)	• Rod photoreceptor axonal retraction and rod-bipolar and horizontal cell synaptic loss, via LIMK/cofilin and actin-myosin light chain-mediated cell contraction [42, 78–81] • Increased expression of TGF-β leading to vitreous collagen gel contraction, proliferation of RPE cells and myofibroblastic transdifferentiation leading to proliferative vitreoretinopathy (PVR) [68, 82]	• Reduced activation of LIMK/cofilin pathway and reduced phosphorylation of myosin light chain, leading to prevention of synaptic retraction and photoreceptor death [41, 78–81] • Decreased proliferation and contractile force of RPE cells [82], decreased proliferative membrane formation and contraction [68]	• Y-27632 • Fasudil [68, 78, 79, 82]	Salamander and porcine models of retinal detachment: RKI reduced rod photoreceptor axonal retraction and reduced rod cell degeneration; Rabbit models of PVR: fasudil reduced PVR and membrane contraction [68].	Fontainhas et al. (2008), Fontainhas et al. (2011), Wang et al. (2015), Wang et al. (2016), Townes-Anderson et al. (2017), Kita et al. (2008), Zheng et al. (2004), Yamaguchi et al. (2017)
Retinoblastoma (Rb)	• Rb cells have increased expression of ROCK proteins, particularly ROCK-1 isoform • ROCK-1 is involved in invasive ability of Rb cells, via actin-myosin mediated processes of cellular adhesion, motility, and proliferation • Process involving LIMK2/cofilin phosphorylation	Selective inhibition of ROCK-1-induced phosphorylation of LIMK2 and cofilin decreases the invasive ability of Rb cells	Y-27632 and ROCK-1 siRNA	Y79 cell lineage of human Rb has shown RKI-reduced LIMK2 and cofilin phosphorylation and reduced cell mobility. ROCK-1 siRNA but not Y-27632 decreased adhesion and invasiveness of Rb cells. Y-27632 did not decrease Rb cell proliferation.	Wang et al. (2014)
Retinitis pigmentosa (RP)	Photoreceptor degeneration and apoptosis via caspase-dependent pathway and overexpression of Bcl-2	Neuroprotective effects with protection of photoreceptor cell apoptosis, with reduced	Y-27632 (intravitreal)	Rat model of RP (Royal College of Surgeon rats) showed preserved a- and b-wave amplitudes in electroretinogram, preserved outer nculear layer thickness, and lower number of apoptotic photoreceptors	Zhang et al. (2015)

(NAION) [107], and an optical coherence tomography angiography (OCT-A) study in patients with glaucoma showed that parapapillary vessel density and prelaminar flow index increased after 2 months of RKI therapy, which suggests improved ONH blood flow [94].

Clinical evidence of RKIs in glaucoma

The first evidence to support the role of Rho signaling pathways in glaucomatous eyes was the detection of increased RhoA levels in the ONH of eyes with glaucoma compared to age-matched controls [108]. Further evidence has been obtained with studies using RKI; more recently, a number of clinical trials have been published in the literature regarding the use of RKI molecules for the control of IOP and glaucoma [88–91, 96–98, 109, 110], which has been reviewed in a recent major review paper [46], and a number of RKI molecules are already being tested in clinical trials [103].

Taken altogether, findings from clinical trials led to FDA approval of netarsudil and ripasudil for the treatment of POAG, given its good efficacy and safety profiles. RKIs produce a stable reduction in IOP both as monotherapy or in combination with other treatments [55], although their clinical utility is likely as adjunctive treatment. Ripasudil has also shown to produce significant, additional IOP-lowering benefit (approximately 3 mmHg) in patients on maximal tolerated medical therapies [48, 55, 92, 93]. The interest in RKIs as adjunctive therapy has led to the creation of a fixed combination of netarsudil and latanoprost, which showed additional IOP-lowering benefit in two large clinical trials (MERCURY-1, MERCURY-2, unpublished data) and is currently pending FDA approval, with an ongoing large phase 3, randomized clinical trial (MERCURY 3, unpublished data).

Rho kinase inhibitors decrease IOP by improving conventional outflow through the TM, and RKIs with norepinephrine transport inhibition properties such as netarsudil also act by reducing AH production and decreasing episcleral venous pressure [42, 43, 84]. The effects of RKI in glaucoma and relevant side effects of topical RKIs [46, 95] are presented in Tables 1 and 2.

Rho kinase inhibitors in secondary glaucoma

Whether patients with secondary forms of open-angle glaucoma derive clinical benefit from topical RKI therapy is controversial.

Proposed pathological mechanisms in pseudoexfoliation glaucoma (PXG) involve trabecular deposition of exfoliative material and increased resistance to AH outflow. RKI has been shown to cause disruption of TM cell adhesions and increase outflow, but clinical benefit of RKI in PXG remains controversial. While some authors found that RKIs reduced IOP in patients with exfoliation glaucoma refractory to prostaglandin analogues [47, 49], other studies have not corroborated this finding [48, 50].

The clinical utility of RKIs in uveitic glaucoma has also been studied. In uveitic glaucoma, obstruction of the trabecular spaces by inflammatory cells, proteins, and fibrin cause increased outflow resistance and trabecular endothelial cell death by phagocytosis and autolysis [52]. ROCK signaling has been implicated in the pathophysiology of anterior ocular inflammation and associated disruption of the blood-aqueous barrier. ROCK pathway leads to downregulation of anti-inflammatory cytokines IL-17 and IL-21 and increases expression of matrix metalloproteinases which leads to increased permeability of the non-pigmented ciliary epithelial cells [53]. Use of RKI has shown experimentally to increase AH outflow, decrease in anterior chamber inflammation, and reduced IOP [53]. However, clinical studies of topical RKI therapy in uveitic glaucoma has produced conflicting results, with some authors showing decreased IOP and ocular inflammation [52], but others not showing clinical benefit of adjunctive RKI therapy [50].

The pathophysiology of corticosteroid-induced glaucoma involves increased TM stiffness and increased TM cell expression of protein zonula occludens 1 (ZO-1) [52]. Furthermore, dexamethasone has been shown to increase RhoA activation in the TM [27, 54]. This mechanism suggests a potential role for RKIs in the treatment of steroid-induced glaucoma; however, clinical findings have been conflicting as for uveitic glaucoma [50, 52].

In vitro evidence in porcine models of pigment dispersion glaucoma (PDG) has shown that inhibition of ROCK signaling effectively increased outflow facility by 38.25% and reduced IOP by 33.58% [51]. It was proposed that RKI induced disruption of TM actin stress fibers, a mechanism common to both POAG and PDG, and also that RKI increased the percentage of phagocitically active cells in the TM, reversing the antiphagocytic effect of pigment exposure [51]. This study has shown that RKI ocular hypotensive effects are not mediated by changes in TM cell motility [51].

RKI may also improve surgical outcomes in glaucoma patients. Studies using in vivo rabbit models of trabeculectomy treated with RKIs showed improved outcomes, with less post-surgical scarring [37, 38]. This may be due to inhibition of TGF-β, an important molecule involved in the activation of Tenon's fibroblasts and cell contraction [36, 39].

RKIs in vitreoretinal diseases

Recent understanding of the role of Rho/ROCK signaling pathways in the pathogenesis of the neural retina and the retinal vasculature has led to increasing clinical research of RKIs in the treatment of retinal disease.

Table 2 Current clinical applications of Rho kinase inhibitors (RKIs) in Ophthalmology

Drug name	ROCK selectivity	Potency against ROCK-1 and ROCK-2 isoforms (nM)	Clinical use in humans	Reported outcomes	Reported adverse effects	Additional comments	References
Y-27632	Dual ROCK-1/2 inhibitor	Ki against ROCK-1 = 140 nM; Ki against ROCK-2 = 300 nM [83]	• Descemetorrhexis without endothelial keratoplasty (DWEK) • Cultured human corneal endothelial cell (CEC) injection in the anterior chamber (AC)	Topical Y-27632 as rescue therapy in patients submitted to DWEK improved corneal transparency, visual acuity, and quality of vision [23]. Injection of cultured CEC into the AC combined with Y-27632 resulted in significant restoration of corneal transparency, visual improvement of 2 or more Snellen lines, and corneal thinning at 6 months; the beneficial effects were maintained at 2-year follow-up [24].	No significant adverse effects were reported.	Y-27632 has shown much lower in vitro potency to disrupt actin fibers and focal adhesions in experimental trabecular meshwork cells compared to netarsudil [84].	Moloney et al. (2017), Kinoshita et al. (2018)
Y-39983/SNJ-1656	Dual ROCK-1/2 inhibitor	Ki against ROCK-1 = 28 nM; Ki against ROCK-2 = 2.4 nM [85]	• Ocular hypertension (OHT) • Primary open-angle glaucoma (POAG)	Phase 2 clinical trial found statistically significant IOP reduction at day 7 compared to placebo (2.2 to 4.0 mmHg reduction from baseline, dose-dependent effect).	Ocular: conjunctival hyperemia, conjunctival hemorrhage, punctate keratitis; systemic: mild hepatic dysfunction, headache, abdominal pain, nasopharyngitis	–	Inoue et al. (2015)
Verosudil (AR-12286)	Dual ROCK-1/2 inhibitor	Ki against ROCK-1 and ROCK-2 = 0.2 nM [86]	• OHT • POAG • Pseudoexfoliation glaucoma (PXG)	Phase 2 clinical trial found statistically significant IOP reductions at 3 weeks (4.4 to 6.5 mmHg, dose-dependent effect) in OHT and POAG. AR-12286 did not show significant clinical benefit in PXG [47].	Ocular: conjunctival hyperemia	AR-12286 has been abandoned due to creation of netarsudil, since AR-12286 has shown much lower in vitro potency to disrupt actin fibers and focal adhesions in experimental trabecular meshwork cells compared to netarsudil [87].	Williams et al. (2011), Skaat et al. (2016)
Ripasudil 0.4%	Dual ROCK-1/2 inhibitor	No information of Ki relative to netarsudil. IC50 for ROCK-1 = 19 nM; IC50 for ROCK-2 = 51 nM	• POAG • PXG • Uveitic Glaucoma	• IOP-lowering effect is approximately 2.6 mmHg at trough and 3.7 mmHg at peak [88, 89]	Ocular: conjunctival hyperemia, blepharitis, allergic conjunctivitis	Topical ripasudil may cause transient corneal guttae [95].	Tanihara et al. (2013), Tanihara et al. (2015), Tanihara et al. (2016), Sato et al. (2016), Inazaki et al. (2017), Inazaki et al. (2017), Inoue et al.

Table 2 (continued)

Drug name	ROCK selectivity	Potency against ROCK-1 and ROCK-2 isoforms (nM)	Clinical use in humans	Reported outcomes	Reported adverse effects	Additional comments	References
			• Corticosteroid (CS)-induced glaucoma • DWEK	• Additive effect with timolol (additional 1.6 mmHg reduction at peak) [90, 91] • Additive effect with latanoprost (additional 1.4 mmHg reduction at peak) [90, 91], and up to 2.6–2.8 mmHg (15.5%) • Additional IOP-lowering benefit in patients on maximal therapy [48, 55, 92, 93] • Improved ONH blood flow has been suggested by increased prelaminar blood flow on OCT-A [94] • In PXG [47, 49, 50], uveitic glaucoma [50, 52, 53], and CS-induced glaucoma, clinical results have been conflicting [50, 52]. • Topical ripasudil as rescue therapy in patients submitted to DWEK improved corneal transparency, visual acuity, and quality of vision [23].			(2017), Yamada et al. (2017), Yasuda et al. (2017), Komizo et al. (2018), Skaat et al. (2016), Matsumura et al. (2017), Chihara et al. (2018), Moloney et al. (2017)
Fasudil 1.2%	Dual ROCK-1/2 inhibitor	Ki for ROCK-1 = 76; Ki for ROCK-2 = 47 [87]	• OHT • POAG • Refractory diabetic macular edema (rDMO)	• Fasudil showed a significant, dose-dependent IOP reduction in a small case series of end-stage POAG patients with uncontrolled IOP [96]. • 2 case series of patients with rDMO demonstrated clinical improvement in retinal edema and in visual acuity when	–	Fasudil has shown much lower in vitro potency to disrupt actin fibers and focal adhesions in experimental trabecular meshwork cells compared to netarsudil [87].	Pakravan et al. (2017), Amadieh et al. (2013), Nourinia et al. (2013)

Table 2 (continued)

Drug name	ROCK selectivity	Potency against ROCK-1 and ROCK-2 isoforms (nM)	Clinical use in humans	Reported outcomes	Reported adverse effects	Additional comments	References
				intravitreal fasudil was combined with intravitreal anti-VEGF drugs [71, 72].			
Netarsudil 0.02%	Dual ROCK-1/2 inhibitor and norepinephrine transport inhibition (Net) [41, 42]	Ki for ROCK-1 = 1; Ki for ROCK-2 = 1 [87]. The active metabolite M1 has 5-fold potency.	• OHT • POAG	• Average IOP reduction 5.7 mmHg at 28 days. • Non-inferiority to latanoprost only demonstrated for patients with baseline IOP < 26 mmHg [97]. • Non-inferiority to timolol maleate only demonstrated for patients with baseline IOP < 25 mmHg [98]. • Fixed combination of netarsudil/latanoprost showed additional 1.6 mmHg IOP-lowering benefit compared to latanoprost alone at 1 year (MERCURY-1, MERCURY-2, unpublished data).	Ocular: conjunctival hyperemia (51–63%); conjunctival hemorrhage (13–18%); vortex keratopathy (13.5–17.5%); pruritus (9–11%); punctate keratitis (5–7.5%); increased lacrimation (7–8%); reduced visual acuity (5.5%); instillation site pain (23–25%)	Fixed combination netarsudil 0.02%/latanoprost 0.005% is pending FDA approval.	Bacharach et al. (2015), Serle et al. (2018), MERCURY-1, MERCURY-2, MERCURY-3 trials (unpublished data)
AMA0076	Dual ROCK-1/2 inhibitor (soft ROCK inhibitor)	Relative potency was similar to Y-39983 and 30-fold more potent than Y-27632 [99].	• OHT • POAG	A phase 1b study showed significant decrease in mean diurnal IOP compared to placebo [100].	No severe adverse effects were reported, and ocular side effects were transient.	No published clinical data is available.	Clinical trial (unpublished data)
ATS-907	Dual ROCK-1/2 inhibitor; prodrug	No information of Ki relative to netarsudil; Ki against ROCK-1 = 36 nM; Ki against ROCK-2 = 37.5 nM; the primary metabolite showed higher potency [101].	• OHT • POAG	Unpublished data from a phase 2 clinical trial.	–	No clinical data is available.	Kengatharan et al. (2011), clinical trial (unpublished data)
INS-117548		No information of Ki relative to	• OHT • POAG	Unpublished data from a phase 2 clinical trial.	Significant ocular adverse effects at higher doses:	No clinical data is available.	Cholkar et al. (2015), Peterson et al. (2008),

Table 2 (continued)

Drug name	ROCK selectivity	Potency against ROCK-1 and ROCK-2 isoforms (nM)	Clinical use in humans	Reported outcomes	Reported adverse effects	Additional comments	References
	Dual ROCK-1/2 inhibitor	netarsudil; Ki against ROCK-1 = 14.4 n-M; Ki against ROCK-2 = 5.8 nM [102].			conjunctival hyperemia, conjunctival hemorrhage, chemosis [103]		clinical trial (unpublished data)

Evidence for the potential role of RKIs in retinal diseases is presented in Table 1. The information about RKIs already studied in patients with retinal disease is presented in Table 2.

Diabetic retinopathy

Diabetic retinopathy (DR), a leading cause of blindness worldwide, is characterized by a microangiopathy which pathogenesis involves hyperpermeability, angiogenesis, microthrombosis, and inflammation; in addition, DR shows several characteristics of a chronic neurodegenerative disease involving RGCs, retinal glial cells, photoreceptors, and RPE. These complex pathogenic mechanisms of disease might explain the high number of cases of diabetic macular edema (DMO) that are refractory to current intravitreal anti-VEGF therapies, and in many of these cases, intravitreal corticosteroid therapy may not achieve the intended anatomical and functional outcomes.

Experimental studies have demonstrated that the Rho/ROCK pathway is involved in the pathogenesis of DR, with activation of ROCK-I in the retinal endothelial cells and RPE [56]. Experimentally induced hyperglycemia induces leukostasis and leukocyte adhesion to the retinal microvasculature via ROCK signaling, inducing inflammation and disruption of the blood-retinal barrier. In addition, hyperglycemia-related ROCK pathway activation causes inactivation of endothelial nitric oxide synthase (eNOS), causing direct microvascular endothelial cell damage [60, 62]. Hypoxic and metabolic changes in diabetes also lead to Muller cell morphological changes, dysfunction, and apoptosis [63, 64]. Finally, the diabetic milieu induces expression of platelet-derived growth factor BB (PDGF-BB) in the retina by vessel pericytes and the expression of PDGF-BB receptors on retinal vessels, which in turn leads to activation of the ROCK pathway and increased vascular endothelial growth factor (VEGF) production [61]. VEGF, a major player molecule in the pathophysiology in retinal neovascularization in diabetic retinopathy, in turn increases ROCK signaling in human retinal microvascular endothelial cells, promoting endothelial cell migration and retinal neovascularization.

RKIs have been shown to increase eNOS expression in retinal endothelial cells and to inhibit leukostasis and leukocyte adhesion, thus preventing retinal vascular endothelial cell damage in in vitro studies and in animal models of both early and late DR [60, 66]. In addition, RKIs in animal models of DM and in rats submitted to retinal ischemia demonstrated decreased RGC loss [60, 67, 70]. RKI has also shown to reduce the expression of VEGF in retinal vessel pericytes [61], preventing capillary dropout secondary to retinal hypoxia. RKI has shown to inhibit VEGF-induced endothelial cell proliferation and migration in animal and in vitro human studies, which suggests that these molecules may prevent retinal neovessel formation [69].

Retinal venular vasomotor tone plays a critical role in post-capillary pressure and capillary fluid exchange. Retinal venous vasoconstriction is mediated, at least in part, by endothelin (ET) molecules, in particular ET-1, and ET-1 has been shown to be increased in the aqueous and vitreous humor of patients with diabetes [57, 58]. Endothelin-mediated vasoconstriction has been implicated in the pathophysiology of retinal edema in diabetic retinopathy and retinal vein occlusions; ROCK signaling appears to independently mediate venoconstriction to ET-1 [59]. In vitro evidence has shown that RKI abolished ET-1-induced venular constriction, suggesting that RKIs relieve vasoconstriction and may reduce retinal edema [59].

Two small prospective, interventional case series have evaluated the anatomical and functional outcomes of RKIs in medically refractory DMO. Combined intravitreal injection of bevacizumab and fasudil, a potent, selective RKI, led to significant improvement in visual acuity and significant reduction in central macular thickness at 4 and 6 weeks post-treatment [71, 72].

Age-related macular degeneration

The neovascular form of age-related macular degeneration (NVAMD), another major cause of impaired vision in developed countries, has been treated with intravitreal injection of anti-VEGF agents. However, the pathogenesis of NVAMD involves not only the choroidal neovascular (CNV) changes but also inflammatory changes which lead to subretinal fibrosis and progressive retinal degeneration, and evidence that anti-VEGF therapy reduces fibrosis and inflammation is limited.

The ROCK pathway is involved in both angiogenesis and inflammation in AMD. ROCK2 signaling is increased with aging, and this results in the overt expression of proangiogenic M2-like macrophages [73]. In human AMD CNV membranes, RhoA, ROCK isoforms, and downstream molecules are expressed in abnormal neovessels, but not in normal ones [73]. The role of macrophages in AMD has been increasingly understood, and evidence has raised the hypothesis that AMD may be associated with immunomodulation and immune imbalance [73, 74]. ROCK signaling is involved in macrophage polarization, and ROCK2 increased signaling with aging leads to an increased M2-macrophage immune response, causing a shift in the normal balance of predominating M1-like macrophages in the retina.

There is experimental evidence in in vitro human CNV membranes that show a potential role for RKI in the treatment of NVAMD. Dual ROCK1/2 inhibition was associated with a 60 reduction in CNV membrane lesion size compared to controls [73]. In addition, RKIs have been shown to be effective in reducing fibrosis in a mouse model of CNV, perhaps by blocking the transforming growth factor (TGF-β)–induced subretinal fibrosis [75]. Interestingly, specific ROCK2 targeting with novel RKI molecules (KD025) may be more effective in AMD, since it targets macrophage plasticity. One study found that selective ROCK2 inhibition led to suppressed M2-macrophage polarization and increased M1-macrophage polarization, thus restoring the normal macrophage balance of the healthy retina [74]. These findings were associated with reduced expression of IL-4 and reduction in CNV membrane size.

Human embryonic stem cell–derived retinal pigment epithelium (hESC-RPE) and induced pluripotent stem cell (iPSC) transplantation has been increasingly studied as a potential therapy for the treatment of geographic atrophy (GA) in AMD and other RPE cell diseases. RPE transplantation is limited by a number of complications, including the epithelial-mesenchymal transition (EMT) switch. ROCK has been implicated in the stimulation of EMT and dynamic regulation of the cytoskeleton, and inhibition of the ROCK signaling pathway has shown to prolong hESC-RPE and iPSC-RPE proliferation capability by reducing TGF-β, a key molecule involved in EMT which is upregulated by ROCK signaling [77]. In addition, specific ROCK-2 inhibition may improve RPE transplant attachment in areas affected by GA, by reorganizing actin fibers in the cytoskeleton, a mechanism possibly related to decreased phosphorylation of cofilin and myosin light chain [76].

Retinal detachment

Rho/ROCK signaling has been shown to be involved in the pathophysiology of retinal detachment (RD). Following RD, photoreceptor cell-bipolar cell synapses are disrupted at the outer plexiform layer [111] due to axonal retraction [112], and although regrowth of the photoreceptor outer segments does occur after surgical reattachment [113], at least some synaptic connectivity is permanently lost. Subretinal and intravitreal administrations of RKI have proved to reduce axonal retraction and photoreceptor cell death after RD in a porcine model of RD [78–81, 114].

Proliferative vitreoretinopathy (PVR) is a potential dreadful complication of RD, being the most frequent cause of re-detachment post-surgical reattachment. Its pathogenesis involves the migration of hyalocytes, RPE cells, and glial cells into the vitreous following detachment, which organize into membranes with contractile properties; these properties may at least be imparted by Rho/ROCK and TGF-β signaling [82, 115]. In an experimental study using vitreous samples of PVR and a rabbit model of PVR, RKIs showed to inhibit proliferative membrane contraction and progression [68]. Given these findings, RKIs might in the future play a role in PVR prevention following RD and following RD surgery.

Other retinal diseases

ROCK signaling has been implicated in other retinal diseases, including retinoblastoma [116] and retinitis pigmentosa [117]. Evidence of the role of RKIs in these diseases is shown in Table 1.

Conclusions

RKIs represent a novel class of drugs with increasing potential for the treatment of several ophthalmic diseases, including anterior and posterior segment diseases as well as glaucomatous optic neuropathy. While these drugs have already been approved for treatment of glaucoma and shown favorable results in large RCTs, their use in corneal disease and retinal disease is still at an early clinical research stage, with seemingly good reported outcomes particularly in corneal endothelial disease. Importantly, the clinical evidence from RKIs highlights the role of translational research of signaling pathways in the eye.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with humans or animals performed by any of the authors.

Literature research We searched the PubMed and Google Scholar databases to identify articles published up to 31 October 2018, using the following key terms: Rho kinase inhibitors in ocular disease, Rho kinase in corneal endothelial disease, Rho kinase inhibitor in glaucoma, and Rho kinase inhibitor in retinal disease. In addition, we manually searched the reference lists of most primary articles and review articles.

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DMEK for the treatment of interface fluid syndrome secondary to failed DSAEK graft: A case report and review of the literature

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ABSTRACT

Purpose: To report a case of Descemet membrane endothelial keratoplasty (DMEK) for the management of post-laser in situ keratomileusis (LASIK) interface fluid syndrome (IFS) secondary to failed Descemet stripping automated endothelial keratoplasty (DSAEK) graft, and to provide a literature review on endothelial keratoplasty (EK) for this indication.

Observations: A 52-year-old patient presented with LASIK interface fluid accumulation and a non-functioning primary DSAEK graft. Past ophthalmic history was relevant for: (1) phakic intraocular lens (PIOL) implantation with later refinement by LASIK; (2) combined PIOL explantation and refractive lens exchange due to accelerated endothelial cell loss (ECL); (3) primary DSAEK due to corneal decompensation.

A secondary EK graft (DMEK) was performed, and the patient was prospectively followed for 6 months (M6). DMEK surgery was uneventful, without postoperative graft detachment. Corneal clearing and resolution of interface fluid accumulation occurred during the first postoperative month. Best-corrected visual acuity (BCVA) improved from 20/800 Snellen to 20/25 Snellen at 3-month follow-up, remaining stable at M6. Due to a persistent rise in intraocular pressure (IOP), the patient underwent uneventful non-penetrating deep sclerectomy 2 months after DMEK, with controlled IOP and without accelerated ECL.

Conclusions and Importance: DMEK is feasible, effective, and safe in the management of IFS in cases where corneal endothelial failure plays a major role, even in complex eyes with previous EK grafts. Aggressive postoperative IOP control is warranted to decrease the risk of interface fluid recurrence and damage to the optic nerve. Studies with larger patient numbers are encouraged to ascertain the role of EK for this indication.

1. Introduction

Interface fluid syndrome (IFS) is a rare but potentially vision-threatening complication of LASER in situ keratomileusis (LASIK), characterized by the accumulation of fluid in the flap interface. It was traditionally known as pressure-induced stromal keratitis (PISK), but IFS is now more widely used because: 1) although a rise in intraocular pressure (IOP) may be the main mechanism, interface fluid accumulation may occur in eyes with corneal endothelial cell failure without high intraocular pressure (IOP), and 2) the term keratitis is a misnomer, as there is no actual inflammation of keratocytes.[1]

In cases of IFS related to increased IOP, management generally consists of ocular hypotensive drugs and cessation of topical corticosteroids (CS). However, corneal transplantation may be needed when corneal endothelial failure is the main mechanism. To date, reports on endothelial keratoplasty (EK) for this indication are scarce.

We present a complex case of LASIK interface fluid syndrome (IFS) managed with Descemet membrane endothelial keratoplasty (DMEK), and provide a literature review on EK for the management of IFS.

Abbreviations: DMEK, Descemet membrane endothelial keratoplasty; LASIK, LASER in situ keratomileusis; IOP, Intraocular pressure.

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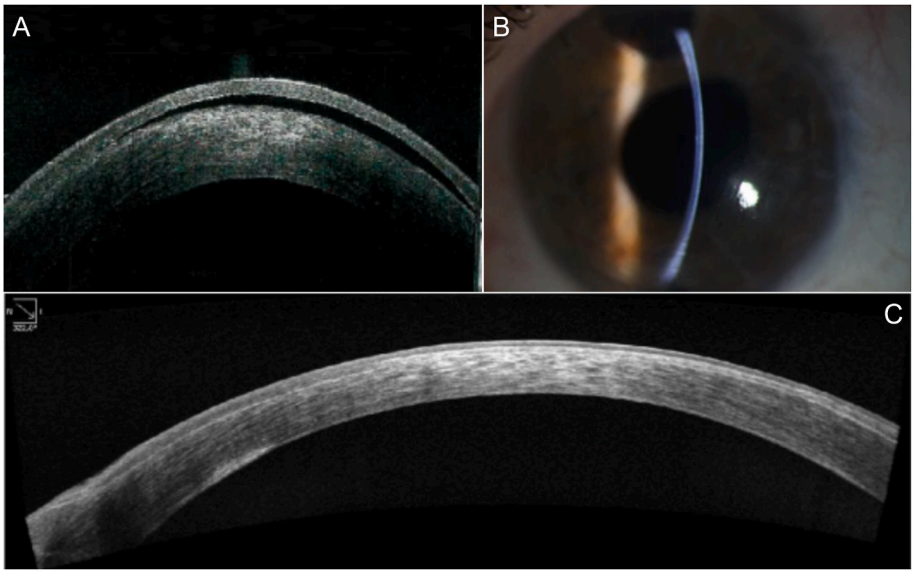


Fig. 1. A. Anterior segment optical coherence tomography (AS-OCT) scan at presentation. Fluid was present at the LASIK interface, and a thickened stromal bed was observed, along with an underlying failed donor DSAEK graft. B. Anterior segment photograph taken 6 weeks after DMEK, showing corneal transparency and central corneal stromal thinning. C. AS-OCT scan performed in the same visit, showing resolution of flap interface fluid accumulation, stromal bed thinning, and an attached functioning DMEK graft.

2. Case report/findings

A patient who underwent DMEK to manage IFS and was prospectively followed for 6 months after DMEK. A 52-year-old woman presented to our Cornea and Refractive Surgery Unit in May 2021 for decreased visual acuity in her left eye (OS). The patient's ophthalmic surgical history showed a combination of bilateral implantation of an angle-supported anterior chamber phakic intraocular lens (PIOL) plus laser in situ keratomileusis (LASIK) in 2006, and PIOL explantation plus refractive lens exchange due to accelerated corneal endothelial cell (CEC) loss in November 2017. Due to irreversible corneal edema, DSAEK was performed in September 2020 with early graft failure, leading to a secondary loss of corneal transparency and accumulation of fluid in the LASIK flap interface that was refractory to multiple medical and surgical therapies, including flap elevation and suturing.

Upon first presentation at our institution, best-corrected visual acuity (BCVA) was 0 logMAR (20/20 Snellen) in OD and 1.6 logMAR (20/800 Snellen) in OS. Diffuse corneal stromal edema with epithelial bullae due to a failed DSAEK graft was observed, with limited visualization of the anterior chamber (AC) details. Although IOP was 12 mmHg with Goldmann applanation tonometry (GAT), glaucomatous optic neuropathy was observed, with significant peripapillary retinal nerve fiber layer (pRNFL) thinning on optical coherence tomography (OCT) and corresponding visual field defect on static automated perimetry testing.

Anterior segment OCT (AS-OCT) scans (provided by the patient) revealed a thickened corneal stromal bed and presence of fluid in the LASIK interface (Fig. 1A).

The decision was to first perform a DMEK. Under local anesthesia, removal of the failed DSAEK donor graft was performed under air. Descemetorhexis was not required, but the recipients' posterior stroma was explored for irregularities and remnants or tags using gentle scraping with our spatula. An 8.0-mm DMEK graft (donor graft endothelial cell density = 3000 cells/mm^2) was inserted using the technique we have previously described,[2] and attached to the host posterior stroma with sulphur hexafluoride 20% (SF6) endotamponade. The postoperative treatment was as previously described for secondary EK.[3]

The DMEK graft was completely attached in the early postoperative period, without early perioperative complications including need for rebubbling and IOP spikes. However, the patient developed a significant rise in IOP of above 30 mmHg 2 months after the surgery, which lasted more than three weeks despite ocular hypotensive drugs (topical and

Table 1
Published reports on endothelial keratoplasty for the treatment of LASIK interface fluid syndrome.

Authors [ref]	Journal (year)	Eyes (n)	EK technique	F–U	Outcome
Hoffmann et al. [4]	J Cataract Refract Surg (2008)	1	DSEK	3 months	DSEK insufficient to solve fluid Required elevation of LASIK flap at 11 weeks, then PKP at 3 months
Luceri et al. [5]	Cornea (2016)	1	DMEK	6 months	Uneventful DMEK; IFS resolved 1 month post-operatively
Shajari et al. [6]	J Refract Surg (2017)	1	DMEK	6 months	Partial GD requiring rebubbling + CME treated topically. IFS resolved at last F–U
Srirampur et al. [7]	Ind J Ophthalmol (2019)	1	UT-DSAEK	6 months	Uneventful UT-DSAEK; IFS resolved 6 months post-operatively
Galvis et al. [8]	Saudi J Ophthalmol (2019)	1	DMEK	2 months	Uneventful DMEK; IFS resolved 5 days post-operatively
Wolf et al. [9]	J Refract Surg Case Rep (2021)	1	Secondary DSAEK (after failed DMEK which induced IFS)	6 weeks after secondary EK	Uneventful DSAEK; IFS resolved 1 week post-operatively
Our study	–	1	Secondary DMEK (after failed DSAEK which induced IFS)	6 months after secondary EK	Uneventful DMEK; IFS resolved in the first postoperative month

Legend: LASIK – LASER in situ keratomileusis; DSEK – Descemet stripping endothelial keratoplasty; DMEK – Descemet membrane endothelial keratoplasty; IFS – interface fluid syndrome; GD – graft detachment; CME – cystoid macular edema; DSAEK - Descemet stripping automated endothelial keratoplasty; UT-DSAEK – ultra-thin DSAEK.

systemic), leading to the decision to perform a non-penetrating deep sclerectomy (NPDS). No major perioperative or postoperative complications occurred after NPDS, and IOP measured by GAT was 6 mmHg 6 months after DMEK (under maintenance of topical CS treatment and without need for hypotensive drops), without progression of pRNFL thinning on OCT.

BCVA improved to 0.15 logMAR (20/32 Snellen) at the one-month postoperative visit, and uncorrected distance visual acuity was 0.1 logMAR (20/25 Snellen) at the 3-month follow-up, remaining stable at the last follow-up, 6 months after DMEK. On slit-lamp examination a clear cornea was observed, with an obvious thinning of the corneal stromal bed (Fig. 1B); central corneal thickness after DMEK decreased from 567 μm to 481 μm, and AS-OCT confirmed resolved interface fluid accumulation (Fig. 1C). Final postoperative CEC density was 2457 cells/mm^2 (18% CEC loss).

3. Discussion

Our case highlights the two main proposed mechanisms of IFS.[1,4] We postulate the patient developed IFS following DSAEK due to a combination of an individual CS-response and a thick, non-functioning DSAEK graft (corneal endothelial failure). The IOP measurements at the time of diagnosis may have been falsely low, as may occur in patients with IFS after myopic LASIK. The fact that the patient developed a significant IOP-CS response after DMEK requiring glaucoma surgery is indirect evidence of the putative role of IOP in our case.

DMEK was successful in our case, in line with the previously published reports on EK for the treatment of IFS (including DMEK, DSAEK or ultra-thin DSAEK) suggesting that DMEK effective for LASIK IFS with an associated endothelial pump failure.[4–9] Although the published evidence is limited and consists only of a few number of cases, taken altogether they suggest that resolution of interface fluid is usually fast after EK, with a success rate of 85.7% and with very few complications (Table 1). Only one of the reported cases showed a DSAEK and flap elevation failure ending with a full-thickness keratoplasty.[4]

We also highlight the surgical complexity of this procedure because of the poor visualization of the AC details, which makes the manipulation and attachment of the DMEK graft surgically challenging. However, DMEK can and should be considered in cases of endothelial decompensation or previous EK graft failure, including complex eyes, as we have previously reported.[10] Finally, we emphasize that careful management of IOP in the early postoperative period in any case but especially after lamellar surgery is important, to avoid the appearance or recurrence of flap interface fluid accumulation and to prevent the possible secondary damage of the optic nerve.

4. Conclusions

In conclusion, DMEK is a surgically feasible and effective procedure for the management of the post-LASIK IFS, even in complex eyes. Further studies with larger sample sizes are needed to ascertain the efficacy and safety of this technique.

Patient consent

Informed written consent was obtained from the patient. This report does not contain any personal information that could lead to the identification of the patient.

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Conflicts of interest

The authors have no financial disclosures (NMC, EA, RP, JPC, JLG).

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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TITLE PAGE

Title: Predictive factors for graft failure after primary DMEK surgery - retrospective cohort study

Short title: Long-term outcomes and complications after DMEK.

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ABSTRACT

Purpose: To determine risk factors for graft failure after Descemet's membrane endothelial keratoplasty (DMEK).

Design:
Setting: Private practice, referral centre for keratoplasty.
Design: Retrospective, case-control study.

Methods:
Patients: Single-surgeon case series of 234 consecutive primary DMEK surgeries performed between 2011 and 2021.
Data collection and variables: Recipient, donor, surgical and postoperative were retrieved from the patients' electronic medical records for analysis.
Main outcome measures: Logistic regression analysis was performed to determine factors associated with primary graft failure (PGF), and Cox regression analysis was performed to determine factors associated with secondary graft failure (SGF).

Results: Twenty-one eyes (8.97%) had PGF after DMEK. In the multivariate predictive model, year of DMEK after mid-2017 (OR=0.178), preoperative visual acuity (OR=7.228), comorbid ocular surface disease (OR=8.799), recipient diabetes *mellitus* (OR=6.047), preoperative intraocular pressure (IOP) over 19.5 mmHg (OR=3.608) and rebubbling (OR=13.260) were strongly associated with PGF; there was a weak statistical but clinically relevant association between intraoperative complications and PGF (OR=3.593; p=0.068).
SGF was observed in 40 eyes (18.8%) at a median F-U of 41.5 months (range: 8-123 months). Rejection episodes (HR=3.403), glaucoma (HR=3.227), severe corneal endothelial disease (HR=4.073) and previous corneal graft (HR=3.867) were significant independent risk factors for SGF. There was a trend towards higher donor graft endothelial cell density and lower risk of SGF (HR=0.502, p=0.082).

Conclusions: Surgeon experience, preoperative vision, ocular and systemic comorbidities, intraoperative complications and rebubbling are independent risk factors for PGF after DMEK. Severe corneal endothelial disease, history of glaucoma, previous corneal graft and rejection are strong, independent risk factors for SGF.

Keywords: Descemet membrane; endothelial keratoplasty; graft failure; risk factors.

INTRODUCTION

Endothelial keratoplasty (EK) is currently considered the gold standard for the management of corneal endothelial disease, particularly Descemet's membrane endothelial keratoplasty (DMEK), given the benefits over penetrating keratoplasty (PKP) and Descemet stripping endothelial keratoplasty (DSEK).[1,2] Since the initial description of the DMEK technique by Melles *et al.*,[3] there has been increasing experience worldwide, with an increasing number of publications on DMEK techniques and outcomes. The number of DMEK surgeries has increased exponentially in recent years: DMEK is the most frequently performed type of corneal transplantation in many reference centres in Europe; and in the United Stated of America, the number of EK surgeries surpassed PKP in 2012 and in 2021 the number of DMEK surgeries matched for the first time the number of DSEK/DSAEK surgeries.[4]

However, DMEK grafts are also at risk of developing graft failure. With increasing numbers of DMEK surgeries performed every year and with longer postoperative follow-up (F-U) times, an increasing number of cases of failed DMEK grafts is to be expected.[5-7] Identifying the factors associated with failure of primary DMEK grafts is therefore relevant. However, since DMEK is a relatively recent technique, literature regarding factors associated with clinical outcomes following DMEK is currently limited, particularly whether indication for surgery influences clinical outcomes after DMEK and what factors may be associated with increased possibility of DMEK graft failure.

The aim of this study was to determine the host, donor, and surgery-related factors associated with the increased possibility of graft failure (both PGF and SGF) following primary DMEK surgery.

METHODS

Study Design and Approval

This was a retrospective, interventional, case-control case series of eyes that underwent primary DMEK from 2011 to June 2021 with a minimum of 3 months

of postoperative F-U. This study was prospectively approved by an institutional review board (*Comisión de Ética e Investigación Médica del Instituto de Microcirugía Ocular; COD IMO 210324-174)*. All patients signed an informed consent for participation in research. The study was conducted according to the tenets of the Declaration of Helsinki.

Patients

Primary DMEK surgeries were identified using the terminology “endothelial keratoplasty (DMEK)” from the institution’s electronic surgery database of a single-surgeon series (J.L.G.) Patients with previous PKP or previous DSEK/DSAEK grafts were included, but not eyes with previous DMEK grafts. Inclusion criteria consisted of patients with ≥ 18 years of age undergoing primary DMEK for primary or secondary CE failure with a minimum of 3-month postoperative F-U. Eyes with previous DMEK grafts, eyes with less than 3 months of F-U, eyes with significant missing data regarding postoperative F-U, and patients without signed informed consent for clinical research were excluded from this study.

Data collection and variables

Data was collected retrospectively from the patients’ electronic medical records (EMRs). The interest variables were PGF (defined as a lack of clearing within the first 3 months following DMEK surgery) and SGF (defined as loss of graft function in eyes with initially functioning DMEK grafts). Recipient’s preoperative data included demographic data; indication for DMEK; clinically graded severity of CE dysfunction (based on slit-lamp biomicroscopy examination); preoperative BCVA (measured using Snellen charts, registered in decimal units in the patients EMRs, and it was collected into the study database in decimal units and then converted to logMAR units); preoperative IOP; morphometric data; ocular comorbidities with limited visual potential (LVP), including amblyopia, pathological anterior segment, corneal comorbid condition and/or severe ocular surface disease, history of glaucoma, history of iris damage (iatrogenic, traumatic, or other iris defects), previous corneal graft (PKP or DSEK/DSAEK),

retinal comorbidities or history of vitrectomy; systemic comorbidities. Ocular tissue donor data included donor age, preservation medium, PT (days), donor graft ECD (cells/mm^2), graft diameter (mm), pre-cut tissue (at tissue bank) or surgeon-prepared tissue. Surgery data included year of primary DMEK surgery; waiting time for surgery (months); type of surgery (standalone DMEK, staged DMEK, triple DMEK, phakic DMEK, or DMEK combined with other procedure); and intraoperative complications. Postoperative data collected included F-U time (months), BCVA, IOP, CCT, ECC (cells/mm^2), graft failure (PGF or SGF), rebubbling, immune rejection (IR) episodes and rejection prophylaxis regimes, significant postoperative IOP elevations, and other postoperative complications.

Statistical analysis

An exploratory analysis of all variables was performed. Continuous variables were described as mean and standard deviation (SD) or as median and interquartile range (P25-P75), depending on whether variables followed a normal distribution. Categorical variables were described as frequencies (%).

Univariate logistic regression was performed to determine factors associated with PGF. The covariables that reached a p-value < 0.20 in the univariate analysis were candidates for the logistic regression model. Logistic regression model assumption, named logit linearity in logit, was verified by generalized additive models. To select the best multivariate models, we applied the Akaike Information Criterion (AIC); we compared different models with different combinations of predictors and chose the one with the lowest AIC value (the lower the AIC, the better the model). The results of this model were expressed as estimates of the *odds-ratio* $(\widehat{OR})$ and the corresponding 95% confidence interval (95% CI).

In non-PGF eyes, univariate survival analysis was performed to determine the variables associated with increased risk of SGF. The covariables that reached a p-value < 0.20 in this analysis were candidates for the multivariate Cox regression analysis. We analysed the proportional hazard functions, assumption of this model, based on the Schoenfeld residuals test. To select the best multivariate models, we applied the AIC criterion and chose the one with the

lowest AIC value. The results of this model were expressed as estimates of the *hazard-ratio* ($\widehat{HR}$) and the corresponding 95% CI.

The statistical analysis was performed using *R Development Core Team* (2019) (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline patient data

Two-hundred and thirty-four eyes were analysed (n = 234). Patient baseline data is presented in Table 1. Mean patient age was 63.8 (12.6) years (51.5% of patients were > 65 years of age), and 66.7% of cases were female patients. The main indication for DMEK surgery was FECD (145 eyes, 62%), followed by PPBK (38 eyes, 16.2%), previous PKP or DSAEK graft (19 eyes, 8.1%), and PIOL- or aphakic AS-IOL related corneal decompensation (18 eyes, 7.7%). The median waiting time for DMEK was 4 (2-6) months (range: 0.2-24 months).

By clinical assessment of severity of CEC dysfunction, 147 eyes (62.8%) had severe disease (severe corneal oedema, subepithelial fibrosis, or bullous keratopathy) and the remainder had mild or moderate disease (87 eyes, 37.2%). Some ocular comorbidity was present in 132 eyes (56.4%), including comorbid corneal disease and/or severe dry eye disease (22 eyes, 9.4%), previous iris damage (45 eyes, 19.2%), history of glaucoma treated medically (37 eyes, 15.8%) or previous glaucoma surgery (16 eyes, 6.8%), retinal disease (67 eyes, 28.6%), amblyopia (18 eyes, 7.7.%).

Median preoperative BCVA was 0.50 (0.30-1.00) logMAR; preoperative BCVA was ≤ 0.52 logMAR (≥ 20/60 Snellen equivalent) in 53.4% of eyes. Preoperative CCT data was available in 126 eyes, with a mean preoperative CCT of 655.0 (83.9) µm. Mean preoperative IOP was 13.3 (4.5) mmHg.

DMEK surgery data, intraoperative complications, and rebubbling

The most performed surgery was standalone DMEK (138 eyes, 59.0%); 73 eyes (31.2%) underwent CLE followed 4 to 10 weeks by DMEK (“staged” or

“sequential” surgery); 10 eyes (4.3%) underwent triple surgery (CLE plus IOL implantation plus DMEK grafting), 8 eyes (3.4%) underwent phakic DMEK; and 5 eyes (2.1%) had DMEK combined with additional procedures other than CLE. Median graft diameter used was 8.0 mm (range: 6.5-9.0 mm).

Some intraoperative complication was encountered in 27 eyes (11.5%). Intraoperative complications included need for anterior vitrectomy in six eyes; graft damage during preparation (either in the eye tissue bank or in grafts prepared intraoperatively) or during injection into the AC in five eyes; difficult graft manoeuvring and apposition in seven eyes; air escape through the glaucoma tube in one eye; posterior positive pressure in four eyes; persistent graft fold in three eyes; a small peripheral partial GD at the end of the surgery in one eye; irregular recipient’s posterior stroma in one eye; and decentred graft in two eyes.

Rebubbling was performed in 46 eyes (19.7%). After rebubbling, a correct apposition of the graft and improvement in corneal oedema was seen in 36 eyes (78.3% success rate).

Postoperative corneal endothelial cell loss, immune rejection, and graft survival

Twenty-six eyes had at least one ECC measurement between 3 and 6 months after DMEK. In these eyes, median (P25-P75) decreased from 2681 cells/mm^2 to 1727 (1333-2103) cells/mm^2, corresponding to a median 35.5 (20.7-48.8) % CEC loss between 3 and 6 months after DMEK. Twenty-nine eyes had an ECC measurement at 1-year follow-up. In these eyes, median (P25-P75) ECC decreased from 2500 (2383-2700) cells/mm^2 to 1520 (1267-1795) cells/mm^2, corresponding to a median (P25-P75) CEC loss of 39.2 (27.1-48.6) % 12 months after DMEK.

Of the eyes without SGF and more than 1-year of postoperative F-U, 82 eyes had at least one ECC measurement after the first postoperative year, performed at a median (P25-P75) F-U time of 60.0 (25.0-83.5) months. In these eyes, median donor graft ECD was 2694 (2500-2800) cells/mm^2, and ECC at last measurement was 1111 (749.3-1495.8) cells/mm^2, corresponding to a median total CEC loss of 58.2 (44.6-70.8) % after DMEK.

Primary graft failure was observed in 21 eyes (8.97%). The proportion of FECD eyes in these cases was 38.1%. Sixteen eyes (76.2%) had some ocular comorbid condition. Twenty eyes (95.2%) had severe corneal oedema or bullous keratopathy, whereas this proportion was 62.8% in the whole cohort of primary DMEK. Preoperative IOP in eyes that developed PGF was 16.5 (6.7) mmHg; 27.8% of cases had a preoperative IOP ≥ 21 mmHg, whereas this proportion was 7.7% in the whole cohort of primary DMEK. Seven cases (33.3%) had intraoperative complications, and 10 of the eyes (47.6%) had postoperative GD requiring rebubbling; an eleventh eye with GD was a case of complete GD.

In the remaining 213 eyes, median postoperative F-U time was 42 (18-72) months. Secondary graft failure was observed in 18.8% of eyes (n = 40). Median time to diagnosis of SGF was 41.5 (18-54) months (range: 8-123 months). The most common causes of SGF were LEGF (16 eyes, 40%), IR (9 eyes, 22.5%), and early graft failure (9 eyes, 22.5%); other causes included glaucoma (3 eyes, 7.5%), iatrogenic CEC loss due to subsequent surgeries (2 eyes, 5%), and infectious keratitis (1 eye, 2.5%). The survival curve for primary DMEK grafts is presented in Figure 1.

Immune rejection episodes were documented in 17 eyes (7.3%). Rejection was defined as any increase in corneal thickness or endopigment change, with or without the presence of cells in the AC, as defined by Bonnet *et al.*[8] Median F-U at the time of the IR episode was 34 (23-48) months, but IR episodes occurred between 6 and 117 months after DMEK. Ten of the 17 eyes with IR episodes (58.8%) were not on IR prophylaxis at the time of detection of the episode, which we considered clinically relevant. We performed a sub-analysis of risk factors for IR was made using survival regression analysis (*not shown*). The final multivariate Cox regression model for IR included the variables recipient diabetes *mellitus* (HR = 4.931, p = 0.008), indication for DMEK (FECD or PPBK *versus* other indications; HR = 0.266, p = 0.018), preoperative BCVA (HR = 2.010, p = 0.067) and IR prophylaxis (HR = 0.411, p = 0.083). On univariate analysis, being on IR prophylaxis was strongly associated with a decrease in the risk of IR, with an approximate 64% reduction in the risk of IR episodes (HR = 0.356, p = 0.039). Although IR prophylaxis showed weak statistical

association with IR, it was retained in the final multivariate model because of its clinical relevance (HR = 0.411, p = 0.083).

Factors associated with primary graft failure

Significant covariables in the univariate analysis which were candidates for the multivariate logistic regression model for PGF were the following (Supplemental Table 1): recipient age, non-FECD eyes, more severe CE disease, worse preoperative BCVA, higher preoperative IOP, ocular surface disease, glaucoma, previous corneal graft, year of primary DMEK, recipient diabetes mellitus, intraoperative complications, donor graft ECD, need of rebubbling, and IOP spike in the early postoperative period. A best cut-off point for year of primary DMEK surgery was found, with surgeries performed after mid-2017 having approximately 71% decrease in the possibility of PGF compared to those surgeries performed before that time (OR = 0.294, p = 0.056). There was not a statistically significant association between PT (OR = 1.008, p = 0.950), preservation medium (Optisol-GS, OR = 1.804, p = 0.281), or tissue preparation by the tissue bank (pre-cut tissue OR = 0.533, p = 0.211).

A multivariate model was used to investigate the combined effect of variables on DMEK possibility of PGF. Results of the multivariate logistic regression analysis are presented in Table 2. DMEK surgeries performed after mid-2017 had an 82% lower possibility of PGF compared with surgeries performed before mid-2017 ($\widehat{OR}$ = 0.178, p = 0.045). Comorbid OSD or corneal disease was associated with an 8.8-fold increased possibility of PGF ($\widehat{OR}$ = 8.799, p = 0.008). Recipient diabetes *mellitus* was associated with a 6-fold increase in the possibility of PGF ($\widehat{OR}$ = 6.047, p = 0.010). Preoperative BCVA ≥ 0.56 logMAR was associated with a 7.2-fold increase in the possibility of PGF ($\widehat{OR}$ = 7.228, p = 0.005). Eyes with preoperative IOP ≥ 19.5 mmHg had a 3.6-fold increase in the possibility of PGF ($\widehat{OR}$ = 3.608, p = 0.054). Rebubbling was associated with a 13.2-fold increase in the possibility of PGF ($\widehat{OR}$ = 13.260, p = 0.001). There was a weak statistical but clinically relevant association between presence of intraoperative complications and PGF, with a 3.6-fold increase in the possibility of PGF ($\widehat{OR}$ = 3.593, p = 0.068).

Factors associated with Secondary Graft Failure

Significant covariables in the univariate survival analysis candidates for the multivariate Cox regression analysis (Supplemental Table 2) were recipient age, gender, non-FECD eyes, worse preoperative BCVA, severe corneal oedema or bullous keratopathy in comparison with mild-moderate disease, ocular comorbidities including glaucoma and previous PKP graft, recipient diabetes mellitus, intraoperative complications, rebubbling, IR episodes, and postoperative complications. Donor graft ECD was also significantly associated with SGF, with an approximately 47% lower risk of SGF in cases of DMEK grafts with donor ECD ≥ 2500 cells/mm^2 (HR = 0.528, p = 0.055), which was the case in 78.9% of surgeries; and an ECD cut-off of ≥ 2325.5 cells/mm^2 (as was the case in 91.2% of surgeries) was associated with an even lower risk of SGF (HR = 0.321, p = 0.001). Because there was significant missing data regarding postoperative ECC, CEC loss was not included in the survival analysis.

A multivariate Cox regression model was used to investigate the combined effect of variables in DMEK graft survival, adjusted for all other variables in the model. Table 3 tabulates the clustered Cox model. The variables with a strong statistical association with SGF after DMEK were “rejection”, “glaucoma”, “severity of corneal oedema”, and “previous PKP or DSAEK graft”. Severe corneal oedema or bullous keratopathy before DMEK was associated with a 4.1-fold increase in the risk of SGF ($\widehat{HR}$ = 4.073; p-value = 0.004). Glaucoma was associated with a 3.2-fold increase in risk of SGF ($\widehat{HR}$ = 3.227; p-value = 0.003). Previous corneal graft was associated with a 3.9-fold increase in risk of SGF after DMEK ($\widehat{HR}$ = 3.867; p-value = 0.006). Rejection episodes were associated with an increased 3.4-fold the risk of SGF ($\widehat{HR}$ = 3.403; p-value = 0.001). There was a weak statistical association between donor graft ECD ≥ 2325 cells/mm^2 and SGF, with an approximate 50% decrease in the risk of SGF in cases receiving grafts with ECD above this cut-off ($\widehat{HR}$ = 0.502; p-value = 0.082).

DISCUSSION

In our study, we found an 8.97% rate of PGF after DMEK, which is within the range of 0-12.5% reported by the AAO,[2] and which compares favourably with the 0-29% incidence of PGF after DSEK reported by the AAO.[9] Of note, PGF was the main reason for DMEK failure in two large multicentre analyses.[10,11] Main causes of PGF after DMEK are significant iatrogenic CEC loss (during the preparation, insertion or manipulation of the graft) and GD.[12] Upside-down graft, where the endothelium lies against the recipient's posterior stroma, is a complication now seldom seen with increased surgeon experience and with graft marking techniques to ensure the correct orientation of the graft. Rare causes of PGF after DMEK (with estimated incidence below 0.05%) include corneal ulcer, endophthalmitis, fungal keratitis, and haemorrhage.[11,13]

In our cases of PGF, some clinical characteristics stand out: 1) the relatively low proportion of FECD eyes versus non-FECD eyes; 2) a high proportion of eyes had some important ocular comorbid condition; 3) more than 25% of all eyes that had some intraoperative complication during DMEK evolved to PGF; 4) nearly one quarter of eyes that required rebubbling evolved to PGF; 5) Significant postoperative IOP elevations was seen in over a quarter of eyes with PGF, whereas this complication was observed in 11% of the whole cohort.

Our multivariate logistic regression model identified important potential risk factors for PGF after DMEK.[14,15] We highlight that despite rebubbling being a strong independent risk factor for PGF, it was highly effective in restoring graft function in nearly 80% of eyes with postoperative significant GD. Worse preoperative BCVA (≥ 0.56 logMAR) was also associated with an increased risk for PGF. This is possibly an "indirect marker" of eyes with more severe corneal oedema and/or eyes with comorbidities. We found a statistically weak but clinically relevant association between the presence of intraoperative complications and a 3.6-fold increase in the risk of PGF. In addition, there was a significant association between preoperative IOP ≥ 19.5 mmHg and PGF, which we believe may be due to cases of glaucomatous eyes but also the possibility that eyes with higher IOP at the time of surgery are at increased risk of complications (e.g., positive posterior pressure, difficult manoeuvring of the

DMEK graft). In one recent retrospective study of 103 eyes, multivariate analysis found that “difficult surgery” was the only pre- or perioperative variable which predicted increased CEC loss during the first postoperative year after DMEK.[16] Increased surgeon experience likely decreases graft manipulation and thus the risk of increased iatrogenic CEC loss and rebubbling. We have found that surgeries performed after mid-2017 had a very significantly lower risk of PGF compared to those performed before mid-2017, which suggests surgeon experience is associated with lower rates of PGF. This is in line with recently reported findings of the Dutch National Organ Transplantation Registry, where surgery before 2016 and surgical complications were the most important independent risk factors for early graft failure, which the authors hypothesized to be related to the learning curve on a national level.[17] Finally, recipient diabetes *mellitus* was also associated with increased risk of PGF. Although no studies to date have reported this finding, one study reported diabetic recipients have increased CEC loss at a slightly higher risk of graft failure after DMEK.[18] Interestingly, significant comorbid ocular conditions such as previous grafts and pathological AS showed a statistically significant association with PGF in the univariate model but were not retained in the final multivariate model. In addition, we observed no significant associations between preservation media, PT and graft pre-stripping and the risk of PGF. There is increasing evidence that suggests that preservation time, preservation medium, pre-stripping (eye bank graft preparation) and tissue preloading do not significantly influence the CEC loss or the risk of PGF and early graft failure after DMEK.[19-22]

We have observed a 18.8% rate of SGF after DMEK, with a median time to SGF of approximately 3.5 years. In the American Academy of Ophthalmology Report on outcomes and safety after DMEK, the SGF ranged from 0 to 6.3% (postoperative F-U range: 6 months to 8 years).[2] Since DMEK is a relatively recent technique which has been gaining more traction in recent years, few groups other than the Melles [23,24] and the Price groups [25,26] have reported mid- and long-term outcomes after DMEK,[27,28] which is a major strength of our study. Again, in our study all surgeries were performed by a single surgeon, unlike most long-term studies available to date which include multiple surgeons, which may be a confounding factor. The cumulative probabilities of graft survival at 3-

and 5-year postoperative F-U were 91% and 77%, respectively, which are comparable to the available data in the literature (reported rates of 5-year cumulative survival: 75.7-96%).[23-28] Our cumulative survival results at 10-year postoperative F-U are limited by the low number of cases that reached the 10-year mark.

In our study, we have found that IR, previous corneal allograft, glaucoma, and more severe preoperative CE failure were independent risk factors for SGF after DMEK. Although in our study eyes with previous PKP grafts had a higher risk of DMEK failure and IR, DMEK under PKP should be considered in those cases with an increased risk for rejection and failure after repeat PKP ("high-risk PKP", including eyes with vascularized corneas, previous glaucoma surgery, history of IR episodes) and with an acceptable post-PKP refractive error, since performing EK under a failed PKP is associated with a 43% lower risk of IR compared with repeat PKP.[29,30]

In our study, most eyes with IR episodes ended in graft failure, and IR was a strong risk factor for SGF, increasing its risk 3.4-fold. Our findings contrast with those by other authors who have reported that most cases of IR resolve with treatment and that experiencing an IR episode was not a significant predictor of graft failure within 5 years of surgery;[25,31] Hos *et al.* observed that only 16.7% of cases of IR ended in regraft.[31]. We believe the poor outcomes of IR in our study were because most cases had delayed presentation with significant corneal oedema. Our definition of IR also means that some cases may have been diagnosed as suspected IR episodes but may have been really cases of endothelial cell exhaustion.

We also observed a weak protective association between donor graft ECD ≥ 2325 cells/mm^2 (best cut-off point for SGF analysis) and SGF, which was the case with 87% of surgeries. Price *et al.* also reported higher donor graft ECD and better outcomes after DMEK.[25] This is likely because a higher graft endothelial cell reserve means that the postoperative absolute ECC will be higher, assuming that the rate of CEC loss is within the normal values after DMEK. Our findings advocate for the benefits of having donor grafts with higher ECD. One major limitation of our study is the high proportion of missing data for postoperative ECC, which would have been important to improve the predictive

model of SGF, since CEC loss is the main determinant of DMEK graft failure. In our study, median CEC loss was 39.7% during the first year, in agreement with the reported range in the DMEK literature, comparable to other EK techniques (DSEK/DSAEK and UT-DSAEK), and higher than after PKP because of iatrogenic CEC loss during graft preparation and DMEK surgery. In the eyes with ECC measurements after the first postoperative year, median CEC loss was 58% after a median F-U of 60 months, which is in line with other reports of long-term CEC loss.[24-27] In addition, donor clinical data (apart from age) was not included in the analysis since the form provided by the tissue bank does not include these data. In our study, donor age was not associated with PGF, in line with previous studies which have found that higher donor age, donor diabetes *mellitus*, lower donor graft ECD and longer PT did not increase the rebubbling rate or the 6-month CEC loss after DMEK.[18,20,22] However, other authors have reported increased difficulty in DMEK graft preparation in diabetic donors,[32,33] and the *Cologne-Mecklenburg-Vorpommern DMEK Donor Study* (*COMEDOS* study) found that older donor age, donor cataract surgery and donor systemic comorbidities were risk factors for difficult graft preparation.[33]

In conclusion, worse preoperative BCVA, recipient diabetes mellitus, comorbid ocular surface disease, higher preoperative IOP, rebubbling, and surgery performed before mid-2017 were significant predictors of PGF after DMEK; there was also a statistically weak but clinically very important association between intraoperative complications and risk of PGF. Severe CE failure and bullous keratopathy, history of glaucoma, previous corneal grafts and IR episodes were significant, independent risk factors for SGF after DMEK, and there was a trend towards a lower risk of SGF when donor grafts with higher ECDs were used.

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FIGURE CAPTIONS

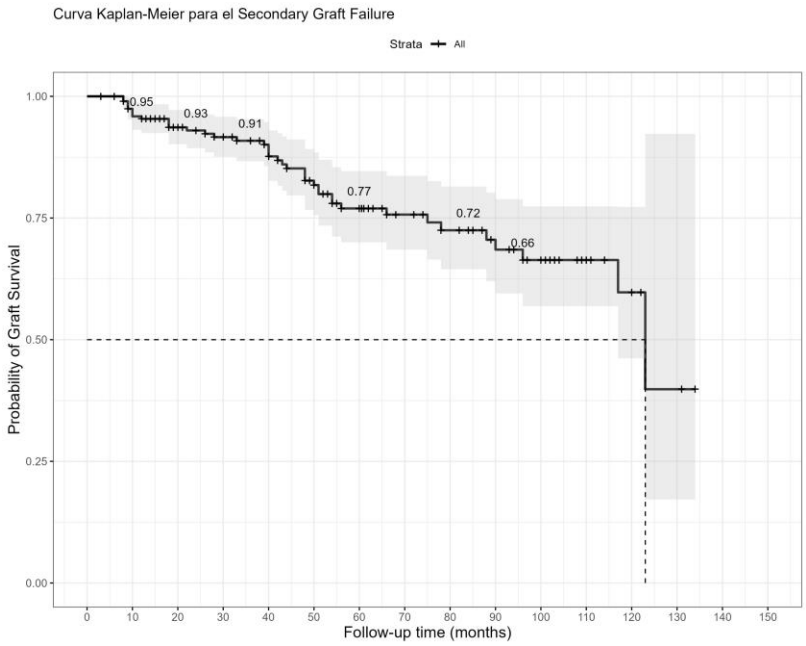


Figure 1 - Kaplan-Meier curve for secondary graft failure after Descemet's membrane endothelial keratoplasty.

Table 1 – Preoperative patient characteristics and ocular tissue donor data (n = 234).

	Variable (units/reference category)		Mean/Median (SD/P25-P75) or Frequencies (n, %)
Recipient data	**Demographic data**	**Gender (female)**	156 (66.7%)
		Age (years)	66.0 (56.0-73.0)
		Laterality (OD)	121 (51.7%)
	Indication for DMEK		
	FECD		145 (62.0%)
	PPBK		38 (16.2%)
	Glaucoma-related		10 (4.3%)
	PIOL- or aphakic AC-IOL related corneal decompensation		18 (7.7%)
	Previous corneal graft (PKP or DSAEK)		19 (8.1%)
	Other indications		4 (1.7%)
	Year of DMEK surgery (before 2016)		102 (43.6%)
	Waiting time for DMEK (months)		4.0 (2.0 – 6.0)
	Waiting time for DMEK < 6 months (Yes)		157 (67.7%)
	Clinical severity of CE disease ("Severity")		
	Mild corneal oedema / non-decompensated FECD		13 (5.6%)
	Moderate corneal oedema		73 (31.2%)
	Severe corneal oedema		83 (35.5%)
	Bullous keratopathy		49 (20.9%)
	Early subepithelial fibrosis		15 (6.4%)
	Categorized variable: Mild-moderate vs ≥ Severe		87 (37.2%) vs 147 (62.8%)
	Preoperative BCVA (logMAR)		0.50 (0.30-1.00)
	Preoperative BCVA ≥0.30 logMAR (≤20/40 Snellen) (Yes)		191 (81.6%)
	Ocular comorbidities	**Ocular comorbidities (Yes)**	132 (56.4%)
		Previous history of glaucoma (Yes)	53 (22.6%)
		Non-surgical glaucoma	37 (15.8%)
		Previous glaucoma surgery	16 (6.8%)
		Pathological AS (Yes)	63 (27.0%)
		Previous iris lesion (yes)	45 (19.2%)
		Corneal comorbid condition or severe DED (Yes)	22 (9.4%)
		Previous corneal graft	
		No previous graft	215 (91.9%)
		Previous graft (PKP or DSAEK)	19 (8.1%)
		Keratoplasty in fellow eye (Yes)	64 (27.4%)
		Retinal comorbidities (Yes)	67 (28.6%)
		No retinal disease	167 (71.4%)
		Retinal disease	50 (21.4%)
		Vitrectomized eye	17 (7.3%)
		Amblyopic eye (Yes)	18 (7.7%)
	Systemic comorbidities (Yes)		120 (53.4%)
	Diabetes mellitus (Yes)		34 (14.5%)

	Prostate disease (Yes) Systemic neoplasm (Yes)	6 (2.6%) 15 (6.4%)
	Preoperative ocular morphometric data	-
	AL (mm) (n = 139)	23.4 (22.6-24.5)
	ACD (mm) (n = 135)	3.2 (2.8-3.5)
	CCT (µm) (n = 126)	640.0 (602.0-698.8)
	Preoperative IOP (mmHg)	12.0 (10.0-16.0)
Donor data	**Age (years)** Donor age < 65 years (Yes)	69.0 (62.0-77.0) 72 (31.7%)
	Graft ECD (cells/mm^2)	2600 (2473-2800)
	Graft diameter (mm)	8.0 (range: 6.5-9.0)
	Preservation medium Cultivated medium Optisol-GS	 195 (84.4%) 36 (15.6%)
	Preservation time (PT, days)	5.0 (5.0-6.0)
	Pre-cut tissue (Yes)	96 (41.6%)
Surgical data		
	Type of Surgery Standalone DMEK Staged DMEK surgery (preceded by CLE) Triple DMEK (combined with CLE) Phakic DMEK DMEK combined with other procedures	138 (59.0%) 73 (31.2%) 10 (4.3%) 8 (3.4%) 5 (2.1%) DMEK + NPDS (1) / DMEK + cut glaucoma tube (1) / DMEK + Salzmann (1) / DMEK + synechiolysis (1) / DMEK + aphakia AS-IOL explantation (1)
	Eyes w/ some intraoperative complication (n,%)	27 (11.5%)
Post-operative data	**GD requiring rebubbling (Yes)**	46 (19.7%)
	Eyes w/ postoperative complications, excluding failure, PCO and rebubbling None Any complication > 1 complication	146 (62.4%) 70 (29.9%) 18 (7.7%)
	Immune allograft rejection episodes (Yes) F-U at diagnosis of IR episode (months) IR prophylaxis at last postoperative F-U (Yes) IR prophylaxis in eyes with IR episodes (Yes)	17 (7.3%) 34.0 (23.0-48.0) (Range 6-117 months) 180 (84.5%) 10/17 (58.8%)
	Primary graft failure (Yes)	21 (8.97%)
	Secondary graft failure (Yes) LEGF IR episodes Early graft failure Glaucoma Other causes	40 (18.8%) 16 (40.0%) 9 (22.5%) 9 (22.5%) 3 (7.5%) 3 (7.5%)
	Postoperative F-U in eyes without PGF (months)	42.0 (18.0-72.0)

Legend: SD – standard deviation; P25-P75 – interquartile range; OD – right eye; DMEK – Descemet's membrane endothelial keratoplasty; FECD – Fuchs' endothelial corneal dystrophy; PPBK – pseudophakic bullous keratopathy; PIOL – phakic intraocular lens; AC-IOL – anterior

chamber intraocular lens; PKP – penetrating keratoplasty; DSAEK – Descemet stripping automated endothelial keratoplasty; CE – corneal endothelium; BCVA – best-corrected visual acuity; AS – anterior segment; DED – dry eye disease; AL – axial length; ACD – anterior chamber depth; CCT – central corneal thickness; IOP – intraocular pressure; ECD – endothelial cell density; PT – preservation time; CLE – crystalline lens extraction; PCO – posterior capsule opacification; IR – immune rejection; LEGF – late endothelial graft failure; F-U – follow-up.

Table 2 - Multivariate logistic regression analysis of factors associated with primary graft failure after Descemet's membrane endothelial keratoplasty.

(N = 217)	OR	IC95% inf	IC95% sup	P-value
Rebubbling [Yes]	**13.260**	**2.944**	**75.352**	**0.001**
Preoperative BCVA [≥ 0.56 logMAR] (Best cut-off)	**7.228**	**2.003**	**32.523**	**0.005**
Comorbid ocular surface/corneal disease [Yes]	**8.799**	**1.729**	**46.161**	**0.008**
Diabetes Mellitus [Yes]	**6.047**	**1.550**	**25.344**	**0.010**
Year of Primary DMEK [≥ 2017.5] (Best cut off)	**0.178**	**0.027**	**0.834**	**0.045**
Preoperative IOP [≥ 19.5 mmHg] (Best cut-off)	**3.608**	**0.962**	**13.454**	**0.054**
Intraoperative Complications [Yes]	3.593	0.882	14.501	0.068
Donor graft ECD [≥ 2576.5 cells/mm^2] (Best cut off)	0.363	0.091	1.287	0.128

Legend: OR – odds-ratio; 95%CI - 95% confidence interval; BCVA – best-corrected visual acuity; IOP – intraocular pressure; DMEK – Descemet's membrane endothelial keratoplasty; ECD – endothelial cell density.

Table 3 – Multivariate Cox proportional hazard regression analysis of factors associated with secondary graft failure after Descemet's membrane endothelial keratoplasty.

(N = 207)	**HR**	**95% CI inf**	**95% CI sup**	**p**
Rejection [Yes]	**3.403**	**1.629**	**7.111**	**0.001**
Glaucoma [Yes]	**3.227**	**1.501**	**6.936**	**0.003**
Severity of corneal oedema [Severe vs mild-moderate]	**4.073**	**1.564**	**10.607**	**0.004**
Previous corneal graft [Yes]	**3.867**	**1.474**	**10.146**	**0.006**
Donor graft ECD [>= 2325.5 cells/mm^2] (Best cut-off for SGF)	0.502	0.231	1.090	0.082
Donor Age [≥ 69.5 years] (Best)	1.930	0.860	4.330	0.111
Diabetes *Mellitus* [Yes]	1.869	0.770	4.539	0.167

Legend: HR – hazard ratio; 95%CI – 95% confidence interval; ECD – endothelial cell density; SGF – secondary graft failure.

Supplemental Table 1 – Univariate logistic regression analysis of factors associated with primary graft failure after Descemet's membrane endothelial keratoplasty.

	Variable (units/reference category)	Mean/Median (SD/P25-P75) or frequencies (n,%)		Univariate analysis		
		Eyes without PGF (n = 213)	Eyes with PGF (n = 21)	$\widehat{OR}$	OR 95% CI	p
Recipient data	**Age (years)**	65.0 (56.0-73.0)	69.5 (64.5-79.5)	1.040	0.999-1.088	**0.068**
	Age ≥ 66.5 years (best cut-off) (Yes)	97 (45.5%)	14 (70.0%)	2.790	1.076-8.132	**0.043**
	Gender (Male)	72 (33.8%)	6 (28.6%)	0.783	0.270-2.017	0.628
	Indication for DMEK: FECD vs non-FECD (non-FECD)	76 (35.7%)	13 (61.9%)	2.929	1.181-7.697	**0.023**
	Indication for DMEK: FECD or PPBK vs other (FECD or PPBK)	171 (80.3%)	11 (52.4%)	0.270	0.107-0.688	**0.005**
	Indication for DMEK: Glaucoma vs FECD (Glaucoma)	10 (4.3%)	7 (3.3%)	7.339	1.339-32.580	**0.011**
	Indication for DMEK: Previous graft vs FECD (Previous graft)	15 (7.0%)	4 (19.0%)	4.567	1.335-16.441	**0.023**
	Indication for DMEK: FECD vs PPBK (PPBK)	34 (16.0%)	3 (14.3%)	1.511	0.318-5.541	0.557
	Preoperative BCVA, logMAR units	0.50 (0.30-1.00)	1.0 (0.50-1.40)	2.276	1.228-4.146	**0.007**
	Preoperative BCVA ≥ 0.56 logMAR (best cut-off) (Yes)	77 (36.2%)	15 (71.4%)	4.416	1.719-12.813	**0.003**
	Preoperative IOP, mmHg	12.0 (10.0-15.5)	17.0 (10.0-20.8)	1.157	1.052-1.275	**0.003**
	Preoperative IOP ≥ 19.5 mmHg (best cut-off) (Yes)	17 (8.4%)	8 (44.4%)	8.753	2.994-25.296	**<0.001**
	Severity of CE decompensation (severe oedema or bullous keratopathy)	127 (59.6%)	20 (95.2%)	13.543	2.744-245.287	**0.012**
	AL, mm	23.50 (22.80-24.60)	22.60 (22.20-23.10)	0.659	0.395-0.997	**0.084**
	ACD, mm	3.20 (2.80-3.50)	2.60 (2.30-3.10)	0.155	0.023-0.777	**0.036**
	ACD ≥ 2.66 mm (best cut-off) (Yes)	106 (82.8%)	3 (42.9%)	0.156	0.029-0.752	**0.020**
	Ocular comorbidities (Yes)	116 (54.5%)	16 (76.2%)	2.676	1.007-8.419	**0.064**
	Comorbid OSD (Yes)	18 (8.5%)	4 (19.0%)	2.549	0.680-7.808	**0.124**
	Previous iris damage (Yes)	35 (16.4%)	10 (47.6%)	4.623	1.800-11.806	**0.001**
	Glaucoma (Yes)	44 (20.7%)	9 (42.9%)	2.881	1.112-7.247	**0.025**
	Glaucoma surgery (Yes)	12 (5.6%)	4 (19.0%)	4.694	1.178-16.002	**0.017**
	Previous PKP or DSAEK graft (Yes)	15 (7.0%)	4 (19.0%)	3.106	0.817-9.734	**0.066**
	Previous DSAEK (Yes)	6 (2.8%)	1 (4.8%)	1.941	0.100-12.307	0.550
	Previous PKP (Yes)	9 (4.2%)	3 (14.3%)	3.882	0.806-14.490	**0.057**

Supplemental Table 1 *(continued)*

	Retinal disease (Yes)	59 (27.7%)	8 (38.1%)	1.606	0.608-4.013	0.318
	Vitrectomized eye (Yes)	14 (6.6%)	3 (14.3%)	2.538	0.537-9.091	0.182
	Pathologic AS (Yes)	50 (23.6%)	13 (61.9%)	5.265	2.099-13.991	**<0.001**
	Systemic comorbidities (Yes)	112 (52.6%)	13 (61.9%)	1.465	0.5928-3.8374	0.416
	Diabetes mellitus (Yes)	27 (12.7%)	7 (33.3%)	3.444	1.214-9.092	**0.015**
Surgery data	**Year of primary DMEK**	2016 (2014-2019)	2015 (2012-2017)	0.871	0.739-1.014	**0.083**
	Year of primary DMEK after June 2017 (best cut-off)	77 (36.2%)	3 (14.3%)	0.294	0.067-0.904	**0.056**
	Waiting time for DMEK (months)	4.0 (2.0-6.0)	3.0 (2.0-5.0)	0.986	0.870-1.083	0.799
	Type of surgery: standalone vs staged or triple DMEK (standalone DMEK)			1.361	0.542-3.723	0.525
	Standalone DMEK	122 (57.3%)	14 (66.7%)			
	Triple DMEK	7 (3.3%)	3 (14.3%)			
	Staged DMEK	70 (39.2%)	3 (14.3%)			
	Phakic DMEK	8 (3.8%)	0 (0.0%)			
	Graft diameter ≥ 8.25 mm (Yes)	4 (2.0%)	1 (5.9%)	3.078	0.153-22.403	0.255
	Intraoperative complications (Yes)	19 (8.9%)	8 (38.1%)	4.825	1.667-13.015	**0.002**
Donor data	**Donor age, years**	69.0 (62.0-77.0)	70.0 (63.0-75.5)	0.999	0.957-1.046	0.964
	Donor graft ECD, cells/mm^2	2600.0 (2500.0-2800.0)	2500.0 (2300.0-2700.0)	0.999	0.997-1.001	**0.196**
	Donor graft ECD ≥ 2576.5 cells/mm^2 (best cut-off) (Yes)	121 (57.9%)	8 (31.1%)	0.448	0.171-1.108	**0.088**
	PT, days	5.0 (5.0-6.0)	6.0 (5.0-7.0)	1.008	0.756-1.276	0.950
	PT ≥ 5.5. days (best cut-off) (Yes)	86 (42.6%)	11 (55.0%)	1.649	0.654-4.258	0.289
	Preservation medium (Optisol-GS)	31 (14.8%)	5 (23.8%)	1.804	0.558-4.994	0.281
	Tissue preparation (pre-cut)	90 (42.9%)	6 (28.6%)	0.533	0.184-1.368	0.211
Early postoperative complications	**Rebubbling (Yes)**	36 (16.9%)	10 (47.6%)	4.470	1.742-11.395	**0.002**
	Significant postoperative IOP elevation 1st month (Yes)	21 (9.9%)	4 (26.7%)	3.307	0.858-10.676	**0.057**

Legend: SD – standard deviation; P25-P75 – interquartile range; PGF – primary graft failure; OR – odds-ratio; 95% CI – 95% confidence interval; DMEK – Descemet's membrane endothelial keratoplasty; FECD – Fuchs' endothelial corneal dystrophy; PPBK – pseudophakic bullous keratopathy; BCVA – best-corrected visual acuity; IOP – intraocular pressure; CE – corneal endothelium; AL – axial length; ACD – anterior chamber depth; OSD – ocular surface disease; PKP – penetrating keratoplasty; DSAEK – Descemet stripping automated endothelial keratoplasty; AS – anterior segment; ECD – endothelial cell density; PT – preservation time.

Supplemental Table 2 – Univariate survival analysis of factors associated with secondary graft failure after Descemet's membrane endothelial keratoplasty.

	Variable (units/reference category)	Mean/Median (SD/P25-P75) or frequencies (n,%)		Univariate analysis		
		Eyes without SGF (n = 173)	Eyes with SGF (n = 40)	$\widehat{HR}$	HR 95% CI	p
Recipient data	**Age (years)**	66.0 (56.0-72.0)	65.0 (54.0-73.0)	0.992	0.967-1.019	0.562
	Age ≥ 58.5 years (best cut-off) (Yes)	120 (69.4%)	23 (57.5%)	0.650	0.347-1.217	**0.178**
	Gender (Male)	72 (33.8%)	66 (38.2%)	0.410	0.171-0.980	**0.045**
	Indication for DMEK: FECD vs non-FECD (non-FECD)	54 (31.2%)	22 (55.0%)	3.206	1.694-6.067	**< 0.001**
	Indication for DMEK: FECD or PPBK vs other (FECD or PPBK)	140 (80.9%)	31 (77.5%)	0.740	0.350-1.565	0.431
	Indication for DMEK: Glaucoma vs FECD (Glaucoma)	6 (3.5%)	1 (2.5%)	2.337	0.309-17.701	0.411
	Indication for DMEK: Previous graft vs FECD (Previous graft)	10 (5.8%)	5 (12.5%)	3.369	1.236-9.181	**0.018**
	Indication for DMEK: PPBK vs FECD (PPBK)	21 (12.1%)	13 (32.5%)	5.119	2.472-10.560	**< 0.001**
	Indication for DMEK: AC-IOL vs FECD (AC-IOL)	14 (8.1%)	2 (5.0%)	0.996	0.229-4.329	0.996
	Severity of CE decompensation (severe oedema or bullous keratopathy)	95 (54.9%)	32 (80.0%)	4.383	2.006-9.575	**< 0.001**
	Preoperative BCVA, logMAR units	0.40 (0.30-0.80)	0.60 (0.30-1.70)	2.847	1.851-4.379	**< 0.001**
	Preoperative BCVA ≥ 0.52 logMAR (theoretical cut-off) (Yes)	83 (48.0%)	25 (62.5%)	2.425	1.270-4.628	**0.007**
	Preoperative IOP, mmHg	12.0 (10.0-15.0)	12.5 (10.0-17.0)	1.057	0.974-1.146	**0.182**
	Preoperative IOP ≥ 21 mmHg (theoretical cut-off) (Yes)	9 (5.4%)	3 (8.3%)	3.165	0.951-10.537	**0.060**
	AL, mm	23.60 (22.80-24.50)	23.40 (22.70-24.80)	0.998	0.976-1.021	0.868
	ACD, mm	3.20 (2.80-3.50)	3.20 (3.00-3.60)	1.310	0.703-2.439	0.395

Supplemental Table 2 *(continued)*

ACD ≥ 2.94 mm (best cut-off) (Yes)	61 (59.8%)	20 (76.9%)	1.835	0.728-4.627	**0.198**
Ocular comorbidities (Yes)	91 (52.6%)	25 (62.5%)	2.037	1.045-3.972	**0.037**
Comorbid OSD (Yes)	15 (8.7%)	3 (7.5%)	0.932	0.286-3.032	0.906
Previous iris damage (Yes)	27 (15.6%)	8 (20.0%)	2.059	0.941-4.503	**0.071**
Glaucoma (Yes)	33 (19.1%)	11 (27.5%)	2.688	1.318-5.481	**0.007**
Glaucoma surgery (Yes)	8 (4.6%)	4 (10.0%)	4.160	1.437-12.044	**0.009**
Previous PKP or DSAEK graft (Yes)	9 (5.2%)	6 (15.0%)	3.539	1.467-8.534	**0.005**
Previous DSAEK (Yes)	5 (2.9%)	1 (2.5%)	2.124	0.287-15.702	0.461
Previous PKP (Yes)	4 (2.3%)	5 (12.5%)	4.075	1.577-10.529	**0.004**
Retinal disease (Yes)	51 (29.5%)	8 (20.0%)	1.081	0.494-2.369	0.845
Vitrectomized eye (Yes)	11 (6.4%)	3 (7.5%)	1.577	0.480-5.174	0.453
Pathologic AS (Yes)	37 (21.5%)	13 (32.5%)	2.292	1.172-4.4834	**0.015**
Systemic comorbidities (Yes)	89 (51.4%)	23 (57.5%)	1.530	0.801-2.924	**0.198**
Diabetes mellitus (Yes)	18 (10.4%)	9 (22.5%)	2.332	1.102-4.936	**0.027**

Supplemental Table 2 *(continued)*

Surgery data	**Waiting time for DMEK (months)**	4.0 (2.0-6.0)	3.8 (2.0-6.0)	1.007	0.922-1.100	0.869
	Type of surgery: standalone vs staged or triple DMEK (standalone DMEK)			1.264	0.651-2.456	0.489
	Standalone DMEK	98 (56.5%)	24 (60.0%)			
	Triple DMEK	7 (4.0%)	0 (0.0%)			
	Staged DMEK	57 (32.9%)	13 (32.5%)			
	Phakic DMEK	6 (3.5%)	2 (5.0%)			
	Graft diameter, mm	8.0 (8.0-8.0)	8.0 (8.0-8.0)	0.402	0.129-1.252	**0.116**
	Graft diameter ≥ 8.25 mm (Yes)	2 (1.2%)	2 (5.7%)	1.732	0.398-7.534	0.464
	Intraoperative complications (Yes)	10 (5.8%)	10 (25.0%)	4.469	2.164-9.228	**< 0.001**
Donor data	**PT, days**	5.0 (5.0-6.0)	5.0 (5.0-7.0)	0.987	0.821-1.188	0.894
	PT ≥ 6.5 days (best cut-off) (Yes)	33 (19.8%)	11 (31.4%)	1.020	0.491-2.119	0.957
	Donor age, years	68.0 (60.0-76.0)	74.5 (66.2-78.0)	1.045	1.011-1.079	**0.008**
	Donor age ≥ 69.5 years (best cut-off) (Yes)	75 (44.1%)	27 (71.1%)	2.869	1.418-5.805	**0.003**
	Donor graft ECD, cells/mm^2	2600.0 (2500.0-2800.0)	2550.0 (2300.0-2697.0)	0.998	0.997-1.000	**0.024**
	Donor graft ECD ≥ 2325.5 cells/mm^2 (best cut-off) (Yes)	156 (91.2%)	26 (68.4%)	0.321	0.160-0.642	**0.001**
	Donor graft ECD ≥ 2500 cells/mm^2 (theoretical cut-off) (Yes)	135 (78.9%)	23 (60.5%)	0.528	0.275-1.014	**0.055**
	Preservation medium (Optisol-GS)	21 (12.3%)	10 (25.6%)	1.124	0.520-2.429	0.766
	Tissue preparation (pre-cut)	83 (48.5%)	7 (17.9%)	0.700	0.296-1.656	0.416
Postoperative data	**Rebubbling (Yes)**	26 (15.0%)	10 (25.0%)	2.002	0.961-4.172	**0.064**
	Significant postoperative IOP elevations (Yes)	18 (10.5%)	3 (7.5%)	0.698	0.213-2.283	0.552
	Immune rejection (Yes)	4 (2.3%)	13 (32.5%)	4.686	2.405-9.131	**< 0.001**
	Postoperative complications (Yes)	50 (28.9%)	17 (42.5%)	2.441	1.210-4.926	**0.013**

Legend: SD – standard deviation; P25-P75 – interquartile range; SGF – secondary graft failure; HR – hazard ratio; 95% CI – 95% confidence interval; DMEK – Descemet's membrane endothelial keratoplasty; FECD – Fuchs' endothelial corneal dystrophy; PPBK – pseudophakic bullous keratopathy; AC-IOL – anterior chamber intraocular lens; CE – corneal endothelium; BCVA – best-corrected visual acuity; IOP – intraocular pressure; AL – axial length; ACD – anterior chamber depth; OSD – ocular surface disease; PKP – penetrating keratoplasty; DSAEK – Descemet stripping automated endothelial keratoplasty; AS – anterior segment; PT – preservation time; ECD – endothelial cell density.

Publication XII

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TITLE PAGE

Title: Predictive factors of long-term visual outcomes after primary Descemet's membrane endothelial keratoplasty (DMEK) - retrospective study.

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ABSTRACT

Purpose: To determine predictive factors of higher levels of best-corrected visual acuity (BCVA) in the long-term after primary Descemet's membrane endothelial keratoplasty (DMEK).

Methods: Retrospective, single-surgeon case series of 129 successful primary DMEK eyes without graft failure and with a minimum postoperative follow-up of 12 months. Mixed effect model for repeated measurements (MMRM) analysis was performed to determine recipient, donor, surgical and postoperative factors associated with BCVA ≤ 0.10 logMAR (≥ 20/25 Snellen).

Results: After primary DMEK, there was a statistically significant improvement in BCVA with a global reduction in logMAR BCVA ($p<0.00001$). There was also a global tendency towards increasing proportion of eyes with BCVA ≤ 0.10 logMAR at all time points ($p<0.00001$), from 1.6% before DMEK to 64.4% in eyes with more than 5 years of F-U. Absence of retinal disease was associated with a decrease of 0.10 logMAR in postoperative BCVA after primary DMEK, maintaining constant the rest of variables ($p<0.001$). The variables age (OR=0.960), postoperative time (OR=1.083), preoperative BCVA ≥ 0.375 logMAR (OR=0.162) and indication for DMEK (OR=5.412) were included in the predictive MMRM model of BCVA ≤ 0.10 logMAR.

Conclusion: Primary DMEK is associated with statistically and clinically significant improvement in BCVA that occur early in the postoperative period and are continuous over time. Eyes with retinal comorbidities have increased risk of worse postoperative BCVA after DMEK. Younger recipient age, Fuchs' dystrophy eyes and eyes with better preoperative BCVA are more likely to achieve postoperative BCVA ≤ 0.10 logMAR.

Keywords: Descemet membrane; endothelial keratoplasty; visual acuity; predictors.

Statements and Declarations:

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INTRODUCTION

Descemet's membrane endothelial keratoplasty (DMEK) is currently considered the standard of care for corneal endothelial disease, considering its advantages over penetrating keratoplasty and Descemet's stripping (automated) endothelial keratoplasty (DSEK/DSAEK) [1]. A high proportion of eyes may expect a rapid visual recovery and to reach high levels of distance best-corrected visual acuity (BCVA) [2-7]. To date, several studies have analysed potential predictors of visual outcomes after DMEK, however with conflicting findings [6,8,12]. Besides, few studies have consistently analysed preoperative and perioperative demographic and clinical factors which may influence graft adherence and function [12]. More importantly, few studies have analysed factors predictive of BCVA over the long-term.

The aim of our study was to determine factors predictive of higher levels of BCVA in the long-term after primary DMEK.

METHODS

Successful primary DMEK eyes with a minimum of 12 months postoperative follow-up (F-U) time were analysed to characterize visual outcomes and to determine routinely analysed data (including recipient, donor, surgical and postoperative data) predictive of higher postoperative BCVA and factors predictive of reaching a BCVA ≤ 0.10 logMAR (≥ 20/25 Snellen). An exploratory analysis of all variables was performed. Continuous variables were described as mean and standard deviation (SD) or as median and interquartile range (P25-P75), depending on whether variables followed a normal distribution. Categorical variables were described as frequencies (%). The proportions of eyes reaching BCVA ≤ 0.30 logMAR (≥ 20/40 Snellen equivalent), BCVA ≤ 0.10 logMAR (≥ 20/25 Snellen equivalent) and BCVA ≤ 0 logMAR (≥ 20/20 Snellen equivalent) were determined at each postoperative F-U time point.

Statistical analysis was performed to assess the changes in postoperative BCVA compared with baseline BCVA (before primary DMEK surgery). To determine the variables associated with postoperative BCVA and with the risk of reaching higher levels of postoperative BCVA after DMEK (BCVA ≤ 0.10 logMAR), we used a mixed effect model for repeated measures (MMRM), which logMAR data from all visits until month 12 as dependent variable, visit as random effect covariate, with subject ID and selected covariates as fixed effect. The restricted maximum likelihood (REML) method of estimation was utilized along with the Kenward-Roger method for estimating the covariance matrix and degrees of freedom. The model used an unstructured covariance (UN) type, thus allowing adjustment for correlations between visits (time points) within subjects. Co-variables included in the mixed model univariate analysis were the following: recipient data (age, gender, indication for DMEK, clinical graded severity of corneal disease, ocular comorbidities with limited visual potential (LVP), systemic comorbidities, preoperative BCVA, CCT and IOP, morphometric data); donor graft data (PT, preservation medium, donor age, donor graft ECD, graft diameter); surgery data (year of primary DMEK surgery, indication for DMEK, waiting time for DMEK surgery, type of surgery, intraoperative complications); and postoperative data (GD requiring rebubbling, significant postoperative IOP elevation during the first postoperative month, IR, and other postoperative complications [excluding posterior capsule opacification and rebubbling]). The covariables that reached a

p-value < 0.20 in the univariate analyses were candidate for the multivariate analysis. To select the best multivariate models, we applied the Akaike Information Criterion (AIC), which balances the goodness of fit and the complexity of the model. The lower the AIC, the better the model. We compared different models with different combinations of predictors and chose the one with the lowest AIC value. These results were expressed as coefficient and the corresponding 95% CI. A second logistic mixed model was built describing variables associated with increased risk of achieving postoperative BCVA ≤ 0.10 logMAR, and the results of this model were expressed as estimates of the *odds-ratio* ($\widehat{OR}$) and the corresponding 95% CI.

The statistical analysis was performed using *R Development Core Team* (2019) (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Evolution of best-corrected visual acuity after DMEK - Descriptive analysis

One-hundred and twenty-nine primary DMEK eyes (n = 129) were analysed to determine factors associated with postoperative BCVA. The evolution of BCVA (logMAR units) during postoperative F-U at different time points is presented in Table 1 and in Figure 1.

Before primary DMEK, the median BCVA was 0.40 (0.20-0.70) logMAR, and the proportion of eyes with BCVA ≤ 0.10 logMAR (≥ 20/25 Snellen) was 1.6%. After DMEK surgery, there was a statistically significant improvement in BCVA, with a global reduction in logMAR BCVA ($p < 0.00001$). Likewise, there was a global tendency towards an increasing proportion of eyes reaching BCVA ≤ 0.10 logMAR (≥ 20/25 Snellen) after DMEK that was statistically significant ($p < 0.00001$). A continuous improvement in BCVA was observed, with increasing probability of reaching BCVA ≤ 0.10 logMAR at each time point. Median postoperative BCVA in eyes with at least 5 years of F-U was 0 (0.00-0.10) logMAR, with 64.4% of eyes reaching BCVA ≤ 0.10 logMAR (≥ 20/25 Snellen) and 54.2% reaching BCVA ≤ 0 logMAR (≥ 20/20 Snellen) at this time point. Eight eyes had a 10-year F-U, all having final BCVA ≤ 0.20 logMAR (≥ 20/32 Snellen) and 62.5% reaching BCVA ≤ 0.00 logMAR.

Univariate analysis of postoperative best-corrected visual acuity

The following covariables were candidates for the multivariate mixed model of postoperative BCVA expressed in logMAR units (Supplemental Table 1): recipient age ≥ 76.5 versus < 72.5 years (best cut-off); indication for DMEK; severity of CE disease; baseline preoperative BCVA; ocular comorbid conditions; history of glaucoma; history of retinal comorbidity; pathological AS; donor age; standalone DMEK versus DMEK and CLE (triple DMEK or staged DMEK surgery); intraoperative complications; rebubbling; rejection; and postoperative complications other than PCO and rebubbling.

The following covariables were candidates for the multivariate logistic mixed model of postoperative BCVA ≤ 0.10 logMAR (Supplemental Table 2): recipient age; indication for DMEK; severity of CE disease; baseline preoperative BCVA; ocular comorbid conditions; history of glaucoma; history of retinal

comorbidity; pathological AS; donor graft ECD ≥ 2447.5 cells/mm^2 (best cut-off); intraoperative complications; rebubbling; rejection; and postoperative complications other than PCO and rebubbling. On univariate analysis, eyes with severe corneal oedema or bullous keratopathy having a significantly lower possibility of reaching postoperative BCVA ≤ 0.10 logMAR (OR = 0.130; p = 0.0003); however, this covariable was not retained in the final multivariate mixed model. Eyes with retinal disease had a significantly lower possibility of reaching postoperative BCVA ≤ 0.10 logMAR (OR = 0.190; p = 0.029) in univariate analysis; however, this variable was not retained in the final multivariate mixed model. On univariate analysis, previous corneal graft did not show a statistically significant association with postoperative BCVA ≤ 0.10 logMAR (OR = 2.450; p = 0.534).

Multivariate analysis of postoperative best-corrected visual acuity

The final multivariate mixed models for postoperative BCVA are presented in Tables 2 and 3. Table 2 shows the multivariate mixed model predictive of postoperative BCVA with respect to baseline preoperative BCVA ("month 0"). Variables in the final model with very strong associations with increased risk for better postoperative BCVA were postoperative F-U time (months) preoperative BCVA (logMAR units), absence of retinal disease, and absence of postoperative complications. There was a significant decrease in logMAR BCVA at every postoperative time point after primary DMEK, compared with baseline BCVA (p < 0.001 at all time points). For each +0.10 logMAR increase in baseline preoperative BCVA, there is a +0.04 logMAR increase in postoperative BCVA (maintaining constant the rest of variables) (Coef = 0.370, p < 0.001). Presence of postoperative complications (other than PCO and rebubbling) was associated with a +0.12 logMAR increase in postoperative BCVA, maintaining constant the rest of variables (Coef = 0.116, p = 0.005). Absence of retinal disease was associated with a decrease of 0.10 logMAR in postoperative BCVA after primary DMEK, maintaining constant the rest of variables (Coef = - 0.101, p < 0.001).

Table 3 shows the multivariate logistic mixed model predictive of postoperative BCVA ≤ 0.10 logMAR (≥ 20/25 Snellen). Although retinal disease showed a statistically significant association with lower possibility of BCVA ≤ 0.10 logMAR on univariate analysis, it was not retained in the final model. Four variables were included in the final model: "patient age", "postoperative time (months)", "preoperative BCVA ≥ 0.375 logMAR (best cut-off)", and "indication for DMEK" being FECD in comparison with other indications. Each month of postoperative F-U was associated with a 1.08-fold increase in the possibility of reaching BCVA ≤ 0.10 logMAR (OR = 1.083; p < 0.001). Eyes with baseline preoperative BCVA ≥ 0.375 logMAR had a 0.16-fold possibility of reaching BCVA ≤ 0.10 logMAR (OR = 0.162; p = 0.003). Fuchs' endothelial corneal dystrophy eyes had a 5.4-fold increase in the possibility of reaching BCVA ≤ 0.10 logMAR compared with other indications for DMEK (OR = 5.412; p = 0.017). There was a very weak statistical association but clinically relevant association between higher patient age and lower possibility of reaching BCVA ≤ 0.10 logMAR, with a 4% lower possibility per each additional year of age (OR = 0.960; p = 0.094).

DISCUSSION

Since the introduction of the DMEK technique by Melles *et al*. [13], it has become clear that DMEK results in rapid visual rehabilitation and superior visual outcomes compared with PKP and with DSEK/DSAEK. In the AAO Report of DMEK safety and outcomes, postoperative BCVA ranged from 20/21-20/31 Snellen (with postoperative F-U ranging from 5.7 to 68 months), and DMEK was superior to DSEK in terms of visual recovery time, visual outcomes, and rejection rates [2]. Several SRMAs, including a Cochrane review, have confirmed that visual outcomes and IR rates favour DMEK over DSEK/DSAEK in eyes with CEC failure, with a trade-off of increased risk of GD and rebubbling [14-16]. With the introduction of the UT-DSAEK technique by Busin *et al*. [17], there has been increasing interest in determining whether outcomes of UT-DSAEK and DMEK are comparable. Our overview of all published SRMAs comparing UT-DSAEK and DMEK concluded that DMEK has superior 12-month visual outcomes (good level of evidence), but UT-DSAEK has a lower rebubbling rate (good quality of evidence) and possibly a lower risk of overall complications (analysis limited by potential bias) [18].

In our retrospective evaluation, we have shown that postoperative BCVA improves significantly over the medium and long-term after DMEK surgery, with increasing proportions of eyes reaching higher levels of BCVA over time. Short-term analysis of visual outcomes has been reported by several groups. In the AAO report of DMEK safety and outcomes, at 6 months 37.6-85% of eyes reached BCVA ≤ 0.10 logMAR, and 17-67% of eyes reached BCVA ≤ 0 logMAR [2]. In the Dutch National Organ Transplantation Registry, at 1-year follow-up 67% of eyes reached BCVA ≤ 0.10 logMAR and 28% reached BCVA ≤ 0 logMAR [6]. However, few groups have reported mid- and long-term outcomes after DMEK, which is a major strength of our study. Besides, in our study all surgeries were performed by a single surgeon, while other studies included multiple surgeons, which may be a confounding factor. Our findings compare favourably with reports with 5- and 8 to 10 years of F-U [7,19-22]. The Melles group has reported mid-term and long-term outcomes after DMEK and found a higher proportion of eyes reaching BCVA ≤ 0.10 logMAR at 4, 5, 7 and 10-year F-U compared with our findings [3,4,23]. However, in these studies the authors excluded eyes with LVP due to ocular comorbidities unrelated to the CEC failure, which explains the differences found in our study, where eyes with LVP were not excluded. Furthermore, the Melles group findings suggest that after 6 months there was no significant improvement in BCVA, but we have found that there is a continuous global improvement in postoperative BCVA over time. Visual improvement over time after EK has also been reported by other authors, hypothesized to be due to continuous, microscopic remodelling of corneal tissue [19,24]. Corneal densitometry studies after DMEK could support our findings [25-27], since there appears to be a continuous improvement in corneal backscatter at least during the first 2 years after DMEK [26], which may explain (at least in part) the room for continuous improvement in visual quality.

In our study, preoperative BCVA, retinal comorbidities and postoperative complications were predictive of worse postoperative BCVA after primary DMEK. Younger patient age, FECD, preoperative BCVA < 0.375 logMAR and postoperative F-U time were independent factors associated with increased possibility of reaching postoperative BCVA ≤ 0.10 logMAR. One study also reported that the chance of reaching excellent postoperative BCVA at 12 months was strongly dependent on preoperative BCVA, with only 40% of eyes with preoperative BCVA of 1.00 logMAR reaching ≤ 0.10 logMAR *versus* 60% for eyes with preoperative

BCVA of 0.30 logMAR [9]. In the Australian Corneal Graft Report 2021/2022, FECD eyes reached superior median postoperative BCVA in comparison with eyes with PPBK or regrafts [28]. Two recent studies corroborate our findings that eyes with CEC failure and retinal disease still derive significant visual benefit from DMEK surgery, although visual outcomes are inferior compared with eyes without macular disease [10,29]. One recent study found that a younger recipient's age was correlated with better visual outcomes following DMEK [30]. However, risk factors for worse visual outcomes after DMEK have been inconsistent, with conflicting findings in the current literature. Proposed pre- and perioperative factors associated with final BCVA after DMEK have included patient age, female gender, diabetic patients, tissue donor age, donor graft ECD, triple DMEK surgery, worse preoperative BCVA, thicker preoperative CCT (more severe corneal oedema), higher preoperative corneal backscatter on corneal densitometry, preoperative macular central thickness, and need for rebubbling [8-12,30]. Some authors have suggested that preoperative Scheimpflug parameters can be predictive of resolution of corneal oedema after DMEK [31,32]. In the Intelligent Research in Sight Registry Analysis, older age, female gender, rebubbling and regrafts were associated with worse postoperative visual outcomes following EK [33]. However, this analysis included both DSEK/DSAEK and DMEK eyes [33].

In conclusion, after DMEK, there is a statistically and clinically significant, continuous improvement in BCVA. Retinal comorbidities and postoperative complications (other than rebubbling and PCO) are risk factors for worse postoperative BCVA after DMEK. Younger patients, eyes with better baseline preoperative BCVA and FECD eyes have a higher possibility of reaching higher levels of postoperative BCVA (≤ 0.10 logMAR) after primary DMEK.

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Compliance with Ethical Standards

Disclosure of potential conflicts of interest: The authors have no conflicts of interest to disclose.

Research involving Human Participants: This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by an institutional review board (IRB) - *Comisión de Ética e Investigación Médica del Instituto de Microcirugía Ocular – CEIm*, study COD IMO 210324-174.

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CAPTIONS

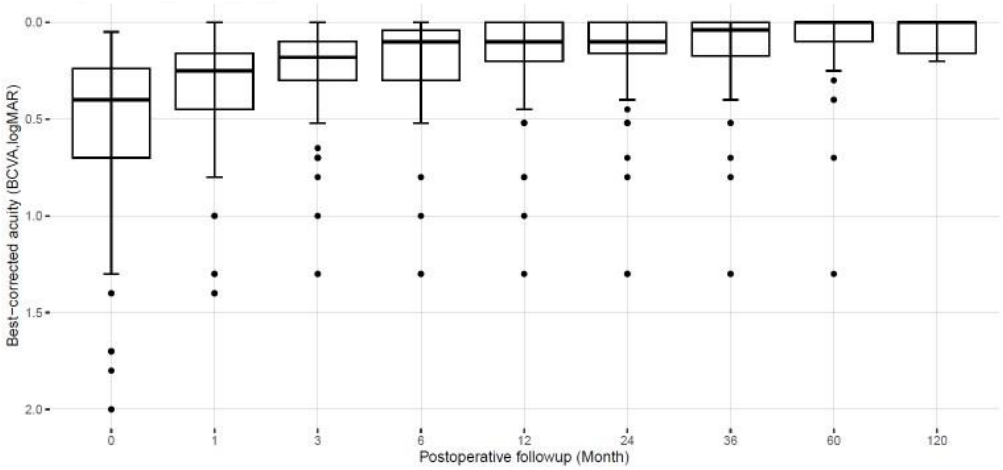


Fig. 1 – Box-plot chart of the evolution of postoperative best-corrected visual acuity after primary Descemet's membrane endothelial keratoplasty

Table 1 – Evolution of postoperative best-corrected visual acuity (BCVA, logMAR units) after primary Descemet's membrane endothelial keratoplasty.

Legend: BCVA – best-corrected visual acuity; SD - standard deviation; 95%CI – 95% confidence interval; Med – median; Min – minimum; Max – maximum; P25;P75 – interquartile range.

Table 2 – Multivariate mixed model of evolution of best-corrected visual acuity after primary Descemet's membrane endothelial keratoplasty eyes.

Legend: Coef – coefficient; 95%CI – 95% confidence interval; BCVA – best-corrected visual acuity.

Table 3 – Multivariate mixed model predictive of best-corrected visual acuity better than 0.10 logMAR after primary Descemet's membrane endothelial keratoplasty eyes.

Legend: OR – odds-ratio; 95%CI – 95% confidence interval; BCVA – best-corrected visual acuity; DMEK – Descemet's membrane endothelial keratoplasty; FECD – Fuchs' endothelial corneal dystrophy.

Supplemental Table 1 – Univariate mixed model analysis of factors associated with postoperative best-corrected visual acuity (BCVA, logMAR units) after primary Descemet's membrane endothelial keratoplasty.

Legend: COEF - coefficient; 95% CI – 95% confidence interval; DMEK – Descemet's membrane endothelial keratoplasty; FECD – Fuchs' endothelial corneal dystrophy; PPBK – pseudophakic bullous keratopathy; CE – corneal endothelium; BCVA – best-corrected visual acuity; IOP – intraocular pressure; AL – axial length; ACD – anterior chamber depth; OSD – ocular surface disease; AS – anterior segment; PT – preservation time ECD – endothelial cell density; PCO – posterior capsule opacification.

Supplemental Table 2 – Univariate mixed model analysis of factors associated with postoperative best-corrected visual acuity ≤ 0.10 logMAR after primary Descemet's membrane endothelial keratoplasty.

Legend: COEF - coefficient; 95% CI – 95% confidence interval; DMEK – Descemet's membrane endothelial keratoplasty; FECD – Fuchs' endothelial corneal dystrophy; PPBK – pseudophakic bullous keratopathy; CE – corneal endothelium; BCVA – best-corrected visual acuity; IOP – intraocular pressure; AL – axial length; ACD – anterior chamber depth; OSD – ocular surface disease; AS – anterior segment; ECD – endothelial cell density; PT – preservation time; PT – preservation time; PCO – posterior capsule opacification.

Table 1 – Evolution of postoperative best-corrected visual acuity (BCVA, logMAR units) after primary Descemet's membrane endothelial keratoplasty.

	Month 0 (N=129)	**Month 1 (N=125)**	**Month 3 (N=123)**	**Month 6 (N=124)**	**Month 12 (N=123)**	**Month 24 (N=110)**	**Month 36 (N=90)**	**Month 60 (N=59)**	**Month 120 (N=8)**	**p**
BCVA (LogMAR)										
N	129	125	123	124	123	110	90	59	8	
Mean (SD)	0.55 (0.46)	0.36 (0.30)	0.25 (0.24)	0.19 (0.22)	0.15 (0.21)	0.15 (0.25)	0.13 (0.24)	0.09 (0.20)	0.06 (0.09)	<0.0001(1)
95% CI	(0.47 ; 0.63)	(0.30 ; 0.41)	(0.21 ; 0.30)	(0.15 ; 0.23)	(0.11 ; 0.19)	(0.10 ; 0.20)	(0.08 ; 0.18)	(0.04 ; 0.15)	(0.00 ; 0.13)	
Med (Min;Max)	0.40 (0.05 ; 2.40)	0.25 (0.00 ; 1.40)	0.18 (0.00 ; 1.30)	0.10 (0.00 ; 1.30)	0.10 (0.00 ; 1.30)	0.10 (0.00 ; 1.30)	0.04 (0.00 ; 1.30)	0.00 (0.00 ; 1.30)	0.00 (0.00 ; 0.20)	
P25 ; P75	0.25 ; 0.70	0.16 ; 0.45	0.10 ; 0.30	0.04 ; 0.30	0.00 ; 0.20	0.00 ; 0.16	0.00 ; 0.18	0.00 ; 0.10	0.00 ; 0.16	
≤ 0.10 LogMAR (n,%)	2 (1.55%)	4 (3.20%)	22 (17.89%)	36 (29.03%)	50 (40.65%)	51 (46.36%)	48 (53.33%)	38 (64.41%)	5 (62.50%)	
≤ 0 LogMAR (n,%)	0 (0.00%)	2 (1.60%)	8 (6.50%)	24 (19.35%)	42 (34.15%)	45 (40.91%)	42 (46.67%)	32 (54.24%)	5 (62.50%)	<0.0001(2)

(1) Kruskal-Wallis rank sum test; (2) Pearson chi-squared test

Legend: BCVA – best-corrected visual acuity; SD - standard deviation; 95%CI – 95% confidence interval; Med – median; Min – minimum; Max – maximum; P25;P75 – interquartile range.

Table 2 – Multivariate mixed model of evolution of best-corrected visual acuity after primary Descemet's membrane endothelial keratoplasty eyes.

(N = 891)		Coef	95%CI inf	95%CI sup	p
Month	1 vs 0	-0.1965	-0.2396	-0.1533	<0.001
	3 vs 0	-0.2945	-0.3378	-0.2512	<0.001
	6 vs 0	-0.3626	-0.4058	-0.3194	<0.001
	12 vs 0	-0.3956	-0.4390	-0.3523	<0.001
	24 vs 0	-0.4022	-0.4469	-0.3574	<0.001
	36 vs 0	-0.3914	-0.4391	-0.3437	<0.001
	60 vs 0	-0.4175	-0.4726	-0.3624	<0.001
	120 vs 0	-0.3866	-0.5172	-0.2559	<0.001
Preoperative BCVA (logMAR)		0.3700	0.3194	0.4206	<0.001
Postoperative Complications	(Yes)	0.1164	0.0343	0.1985	0.005
Retinal Disease	(No)	-0.1007	-0.1557	-0.0458	<0.001

Legend: Coef – coefficient; 95%CI – 95% confidence interval; BCVA – best-corrected visual acuity.

Table 3 – Multivariate mixed model predictive of best-corrected visual acuity better than 0.10 logMAR after primary Descemet's membrane endothelial keratoplasty eyes.

(N = 891)	OR	95%CI inf	95%CI sup	p
Postoperative time (Months)	1.0825	1.0643	1.1010	<0.001
Preoperative BCVA ≥ 0.375 logMAR (Best cut-off) (Yes)	0.1619	0.0489	0.5358	0.003
Indication for DMEK FECD vs non-FECD (FECD)	5.4119	1.3450	21.7755	0.017
Age (years)	0.9602	0.9158	1.0069	0.094

Legend: OR – odds-ratio; 95%CI – 95% confidence interval; BCVA – best-corrected visual acuity; DMEK – Descemet's membrane endothelial keratoplasty; FECD – Fuchs' endothelial corneal dystrophy.

Supplementary Table 1 – Univariate mixed model analysis of factors associated with postoperative best-corrected visual acuity (BCVA, logMAR units) after primary Descemet's membrane endothelial keratoplasty.

	Variable (units/reference category) (N = 129)	Univariate analysis			
		COEF	**COEF 95% CI (lower)**	**COEF 95% CI (upper)**	**p**
Recipient data	**Age (years)**	0.0021	- 0.0012	0.0055	0.214
	Age ≥ 76.5 years *versus* < 72.5 years (best cut-off) (Yes)	0.1284	-0.0038	0.2605	**0.057**
	Indication for DMEK: FECD vs non-FECD (FECD)	0.1596	0.0754	0.2438	**< 0.001**
	Indication for DMEK: FECD or PPBK vs other (FECD or PPBK)	-0.0754	-0.1784	0.0276	**0.151**
	Indication for DMEK: Glaucoma vs FECD (Glaucoma)	0.1567	-0.0953	0.4086	0.223
	Indication for DMEK: Previous graft vs FECD (Previous graft)	0.0141	-0.1571	0.1852	0.872
	Indication for DMEK: PPBK vs FECD (PPBK)	0.2487	0.1237	0.3737	**< 0.001**
	Indication for DMEK: AC-IOL vs FECD (AC-IOL)	0.996	0.229-4.329		0.996
	Severity of CE decompensation (severe oedema or bullous keratopathy)	0.1912	0.1177	0.2648	**< 0.001**
	Preoperative BCVA, logMAR units	0.3972	0.3439	0.4505	**< 0.001**
	Preoperative BCVA ≥ 0.375 logMAR (best cut-off) (Yes)	0.2432	0.1740	0.3124	**< 0.001**
	Preoperative BCVA ≥ 0.52 logMAR (theoretical cut-off) (Yes)	0.2590	0.1907	0.3274	**< 0.001**
	Preoperative IOP, mmHg	-0.0024	-0.0129	0.0080	0.645
	Preoperative IOP ≥ 21 mmHg (theoretical cut-off) (Yes)	0.1685	-0.0400	0.3770	**0.113**
	AL, mm	0.0082	-0.0065	0.0230	0.275
	ACD, mm	0.0279	-0.0440	0.0998	0.447
	ACD ≥ 2.79 mm (best cut-off) (Yes)	-0.0938	-0.1887	0.0011	**0.053**
	Ocular comorbidities (Yes)	0.1506	0.0743	0.2269	**< 0.001**
	Comorbid OSD (Yes)	0.0393	-0.1112	0.1898	0.609
	Comorbid OSD (Yes)	0.154	0.0409	0.2671	**0.008**
	Glaucoma (Yes)	0.1952	0.0888	0.3017	**< 0.001**
	Previous corneal graft (Yes)	-0.0363	-0.2481	0.1756	0.737
	Retinal disease (Yes)	0.2198	0.1355	0.3041	**< 0.001**
	Vitrectomized eye (Yes)	0.2368	0.0905	0.3830	**0.002**
	Pathologic AS (Yes)	0.1737	0.0769	0.2705	**< 0.001**
	Systemic comorbidities (Yes)	0.0172	-0.0632	0.0977	0.675
	Diabetes mellitus (Yes)	0.0651	0.0784	0.2086	0.374

Supplementary Table 1 *(continued)*

Surgery data	**Waiting time for DMEK (months)**	0.0018	-0.0088	0.0124	0.736
	Waiting time for DMEK ≥ 6 months (theoretical cut-off)	0.0015	-0.0852	0.0883	0.973
	Type of surgery: standalone vs staged or triple DMEK (standalone DMEK)	0.1197	0.0386	0.2008	**0.004**
	Graft diameter, mm				
	Graft diameter ≥ 7.875 mm (best cut-off) (Yes)	-0.097	-0.2055	0.0114	**0.079**
	Intraoperative complications (Yes)	0.0553	-0.1363	0.2470	0.572
Donor data	**PT, days**	0.0047	0.0209	0.0304	0.718
	Donor age, years	0.0037	2e-04	0.0072	**0.036**
	Donor graft ECD, cells/mm^2	1e-04	1e-04	2e-04	0.457
Postoperative data	**Rebubbling (Yes)**	0.0153	-0.1075	0.1381	0.807
	Significant postoperative IOP elevations (Yes)	0.0837	0.0493	0.2167	0.217
	Postoperative complications, excluding PCO and rebubbling (Yes)	0.0705	0.0192	0.1602	**0.124**
	Immune rejection (Yes)	0.2234	0.0044	0.4512	**0.055**

Legend: COEF - coefficient; 95% CI – 95% confidence interval; DMEK – Descemet's membrane endothelial keratoplasty; FECD – Fuchs' endothelial corneal dystrophy; PPBK – pseudophakic bullous keratopathy; CE – corneal endothelium; BCVA – best-corrected visual acuity; IOP – intraocular pressure; AL – axial length; ACD – anterior chamber depth; OSD – ocular surface disease; AS – anterior segment; PT – preservation time ECD – endothelial cell density; PCO – posterior capsule opacification.

Supplementary Table 2 – Univariate mixed model analysis of factors associated with postoperative best-corrected visual acuity ≤ 0.10 logMAR after primary Descemet's membrane endothelial keratoplasty.

	Variable (units/reference category) (N = 129)	Univariate analysis $\widehat{OR}$	OR 95% CI (lower)	OR 95% CI (upper)	p
Recipient data	**Age (years)**	0.960	0.920	1.010	**0.124**
	Age ≥ 76.5 years *versus* < 72.5 years (best cut-off) (Yes)	0.010	0.000	0.120	**0.001**
	Indication for DMEK: FECD vs non-FECD (FECD)	0.100	0.030	0.370	**0.001**
	Indication for DMEK: FECD or PPBK vs other (FECD or PPBK)	3.100	0.710	13.580	**0.134**
	Indication for DMEK: Glaucoma vs FECD (Glaucoma)	0.270	0.000	16.000	0.533
	Indication for DMEK: Previous graft vs FECD (Previous graft)	0.240	0.040	1.550	**0.135**
	Indication for DMEK: PPBK vs FECD (PPBK)	0.010	0.000	0.280	**0.005**
	Severity of CE decompensation (severe oedema or bullous keratopathy)	0.130	0.040	0.390	**< 0.001**
	Preoperative BCVA, logMAR units	0.050	0.010	0.220	**< 0.001**
	Preoperative BCVA ≥ 0.375 logMAR (best cut-off) (Yes)	0.080	0.020	0.250	**< 0.001**
	Preoperative BCVA ≥ 0.52 logMAR (theoretical cut-off) (Yes)	0.090	0.030	0.320	**< 0.001**
	Preoperative IOP, mmHg	1.070	0.930	1.230	0.354
	Preoperative IOP ≥ 10 mmHg (best cut-off) (Yes)	3.160	0.950	10.540	**0.061**
	AL, mm	0.960	0.750	1.210	0.710
	ACD, mm	1.030	0.340	3.140	0.962
	ACD ≥ 2.79 mm (best cut-off) (Yes)	8.980	1.880	42.930	**0.006**
	Ocular comorbidities (Yes)	0.370	0.120	1.150	**0.085**
	Comorbid OSD (Yes)	0.830	0.100	6.820	0.866
	Glaucoma (Yes)	0.220	0.040	1.150	**0.072**
	Previous corneal graft (Yes)	2.450	0.150	41.320	0.534
	Retinal disease (Yes)	0.160	0.040	0.600	**0.007**
	Vitrectomized eye (Yes)	0.2368	0.0905	0.3830	**0.002**
	Pathologic AS (Yes)	0.080	0.020	0.380	**0.002**
	Systemic comorbidities (Yes)	1.18	0.390	3.570	0.770
	Diabetes mellitus (Yes)	0.620	0.090	4.470	0.632

Supplementary Table 2 *(continued)*

Surgery data	**Waiting time for DMEK (months)**	0.950	0.810	1.110	0.536
	Waiting time for DMEK ≥ 6 months (theoretical cut-off)	0.850	0.250	2.950	0.802
	Type of surgery: standalone vs staged or triple DMEK (standalone DMEK)	0.100	0.030	0.320	**< 0.001**
	Graft diameter, mm	30.090	2.480	364.52	**0.008**
	Intraoperative complications (Yes)	0.150	0.010	2.600	**0.193**
Donor data	**PT, days**	0.860	0.600	1.230	0.406
	Donor age, years	0.990	0.940	1.040	0.714
	Donor age ≥ 56 vs < 43.5 years (best cut-off)	3.180	0.560	17.940	**0.190**
	Donor graft ECD, cells/mm^2	1e-04	1e-04	2e-04	0.457
	Donor graft ECD ≥ 2477.5 cells/mm^2 (best cut-off)	2.910	0.720	11.840	**0.136**
Postoperative data	**Rebubbling (Yes)**	0.190	0.030	1.140	**0.069**
	Significant postoperative IOP elevations (Yes)	0.0837	0.0493	0.2167	0.217
	Immune rejection (Yes)	0.2234	0.0044	0.4512	**0.055**
	Postoperative complications, excluding PCO and rebubbling (Yes)	0.0705	0.0192	0.1602	**0.124**

Legend: COEF - coefficient; 95% CI – 95% confidence interval; DMEK – Descemet's membrane endothelial keratoplasty; FECD – Fuchs' endothelial corneal dystrophy; PPBK – pseudophakic bullous keratopathy; CE – corneal endothelium; BCVA – best-corrected visual acuity; IOP – intraocular pressure; AL – axial length; ACD – anterior chamber depth; OSD – ocular surface disease; AS – anterior segment; ECD – endothelial cell density; PT – preservation time; PT – preservation time; PCO – posterior capsule opacification.

Publication XIII

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TITLE PAGE

Title: Intraocular lens opacification following Descemet's membrane endothelial keratoplasty – risk factors and outcomes after intraocular lens exchange

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ABSTRACT

Purpose: To determine risk factors for intraocular lens opacification (IOLop) following Descemet's membrane endothelial keratoplasty (DMEK) and to analyse clinical outcomes after IOL exchange.

Methods: Cross-sectional analysis of all cases of IOL exchange due to post-DMEK IOLop with a minimum of 6-month postoperative follow-up (F-U). Main outcomes analysed were change in best-corrected visual acuity (BCVA) after IOL exchange, endothelial cell loss, and graft survival. An historical cohort of 232 pseudophakic DMEK eyes was retrospectively analysed to determine risk factors for post-DMEK IOLop.

Results: Four eyes (four patients) were observed during the study period (median F-U = 45 (35.5-86.8) months). IOL materials were hydrophilic acrylic IOLs in two eyes and hybrid hydrophobic-hydrophilic in the other two. At the study visit, improvement in median BCVA after IOL exchange was statistically significant (0.25 (0.19-0.41) logMAR to 0.00 (0 – 0.10 logMAR); p = 0.041). Endothelial cell loss ranged between 57.7-85.3%, without cases of graft failure.

In the historical cohort, 21 eyes (9.05%) had some IOLop. IOL material data was available in 105 eyes. In multivariate logistic regression model, non-hydrophobic IOLs (OR = 65.5, p = 0.0005) and rebubbling (OR = 9.51, p = 0.0138) were independent risk factors for IOLop following DMEK.

Conclusions: Post-DMEK IOLop is infrequent, but a non-neglectable proportion of cases may require IOL explantation. IOL exchange is safe and effective in these eyes but may pose a risk for increased EC loss. This study confirms that IOL material and number of rebubblings are major risk factors for post-DMEK IOLop.

INTRODUCTION

Descemet's membrane endothelial keratoplasty (DMEK) has become the gold standard technique for the treatment of corneal endothelial disease and failure, with a rapid visual recovery, low risk of allograft rejection, and good medium-term survival rates. The most common complication after DMEK is graft detachment and the need for rebubbling; other postoperative complications (apart from rejection) are less frequent and include increased intraocular pressure (IOP), cystoid macular oedema,[1] and intraocular lens (IOL) opacification. Intraocular lens opacification (IOLop) is an infrequent but likely underreported complication after DMEK, with scarce literature data.[2-4] Post-DMEK IOLop is due to the deposition of calcium and phosphate in the IOL surface and/or subsurface.[3,5,6] There are several proposed risk factors for IOLop after endothelial keratoplasty,[7] with IOL materials with high water content (WC) being the most consistently reported risk factor.[3,4]

Intraocular lens opacification can cause significant impact in vision, and in these cases IOL explantation may be indicated. However, there is limited data available on the incidence of post-DMEK IOLop requiring explantation due to significant impact in visual acuity, and there are no data regarding the long-term visual and graft outcomes following IOL explantation in this setting. The aim of this study was to analyse the long term visual and graft outcomes after IOL explantation due to post-DMEK IOLop, and to determine the risk factors for post-DMEK IOLop.

MATERIALS AND METHODS

This study consisted of a cross-sectional analysis of all cases of IOL explantation due to post-DMEK IOLop with impact in vision that were observed between November 2021 and April 2022 at our institution, and that had a minimum of 6 months of follow-up (F-U) following IOL explantation. Decision to explant an opacified IOL was made based on significant impact in vision, defined as loss of at least 1 line of Snellen visual acuity.

In patients fulfilling the inclusion criteria, electronic medical records (EMRs) were reviewed, and the following variables were collected for analysis: demographic

data (age, gender); IOL model and material; indication for DMEK; ocular comorbidities; donor cornea endothelial cell density (ECD, cells/mm^2); need for rebubbling; time between DMEK surgery and IOLop; best-corrected visual acuity (BCVA) before DMEK and BCVA before IOL explantation. Visual acuity was measured using a Snellen visual chart, and values were converted to logMAR units for statistical analysis.

At the study visit, the following variables were collected and analysed: BCVA ("final BCVA"), ECD and central corneal thickness (CCT) using specular microscopy, slit-lamp assessment of corneal transparency, and assessment of graft survival.

An exploratory analysis of all variables was performed. Continuous variables were described as mean (SD) or as median (IQR), depending on whether variables followed a normal distribution. To determine the statistical significance of the postoperative evolution in BCVA, one-way analysis of variance test was applied. Categorical variables were described was frequencies (%), and chi-square or Fisher's exact test were applied to determine differences. The significance level α was 0.05. The statistical analysis was performed using *R Development Core Team* (2019) (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). The main outcome variable was the change in BCVA after IOL explantation compared with baseline BCVA before IOL explantation. Secondary outcomes were graft endothelial cell (EC) loss and graft survival at the study visit.

To determine risk factors for post-DMEK IOLop, we retrospectively reviewed the EMRs of 232 pseudophakic DMEK eyes (including standalone DMEK eyes and eyes that underwent either sequential or combined crystalline lens surgery and DMEK). The variables collected included gender, age, indication for DMEK, patient diabetes mellitus, history of glaucoma, previous corneal grafts, AL, history of high myopia, ACD, IOL material and WC, and need for rebubbling after DMEK. Regression analysis was performed. Univariate logistic regression was performed to determine factors associated with IOLop. The covariables that reached a p-value < 0.20 in the univariate analysis were candidate for the logistic regression model. Logistic regression model assumption, named logit linearity in

logit, was verified by generalized additive models. To select the best multivariate models, we applied the Akaike Information Criterion (AIC), which balances the goodness of fit and the complexity of the model. The lower the AIC, the better the model. We compared different models with different combinations of predictors and chose the one with the lowest AIC value. The results of this model were expressed as estimates of the *odds-ratio* $(\widehat{OR})$ and the corresponding 95% confidence interval (95% CI).

The study was conducted according to the tenets of the Declaration of Helsinki and was approved by the local Research Ethics Committee (*COD IMO 211022-197*). All patients signed an institutional review board-approved informed written consent for the study.

RESULTS

Cross-sectional study: Outcomes of IOL explantation

During the recruitment period, 117 DMEK eyes of 77 patients attended the visits at our centre. Of those, four eyes of four patients matched the study inclusion criteria. The baseline data of these cases is presented in Table 1. Patient's age at DMEK surgery ranged between 50 and 76 years. Three eyes had some ocular comorbid condition: Patient #1 had history of complex cataract surgery with irregular pupil and glaucoma and underwent repeat DMEK due to early SGF; Patient #2 had a history of complicated cataract surgery with a decentred IOL and ocular hypertension (OHT); and Patient #4 had history of myopic LASIK ablation. In all cases, the ocular endotamponade gas used was SF6 20%. One eye (Patient #1) had history of a previous DMEK graft, whilst the remainder had no previous corneal grafts. Since no eyes had required rebubbling after DMEK, the total number of gas bubbles in the AC was two in Patient #1) and one in the remainder (Patients #2, #3 and #4). Two eyes had hydrophilic acrylic IOLs with 25-26% water content (WC) [Patient #1 Akreos IOL (Bausch and Lomb); Patient #2 Physiol Micro F (PhysIOL)] and the other two eyes (Patients #3 and #4) had hybrid hydrophobic and hydrophilic monomers, the precise WC of which are not reported by the company (Precizon Monofocal, Ophtec). Time between DMEK and detection of IOLop ranged from 2 to 44 weeks, and time between DMEK and

IOL explantation due to significant impact in visual acuity ranged from 11 to 24 months.

Surgery was performed under local anaesthesia and sedation in all cases. All eyes underwent IOL exchange safely: three eyes (Patients #1, #2 and #3) required anterior vitrectomy (patient #2 had a posterior capsule rupture during his cataract surgery at another institution; patients #1 and #3 had a previous Nd: YAG laser capsulotomy), two of which had an iris-claw IOL implanted and the other had a 3-piece IOL implanted in the ciliary sulcus. Patient #4 had a single-piece IOL implanted in the capsular bag.

Visual outcomes of these cases are presented in Table 2. BCVA before last DMEK surgery ranged between 0.18 and 0.80 logMAR. In all cases, a decline of at least one line of BCVA was observed due to postoperative IOLop, with a median BCVA at the time of IOL explantation of 0.25 (0.19-0.41) logMAR. After IOL exchange, visual recovery was observed between postoperative day 1 and 60; one eye had a delayed visual recovery due to postoperative CMO. At the study visit, median F-U after IOL exchange was 45 (35.5-86.8) months (range: 34-99 months). At the study visit, median BCVA was 0 (0.00-0.10 logMAR), which was clinically and statistically significant compared to BCVA prior to IOL exchange ($p = 0.041$).

After IOL explantation, two eyes had OHT requiring hypotensive drops, and one had postoperative cystoid macular oedema which resolved after treatment. At the study visit, all eyes had clear corneas with functioning DMEK grafts. On specular microscopy performed at the study visit (Figure 1), CCT ranged between 462-543 µm (in comparison with the CCT before DMEK surgery ranging between 599-665 µm), and ECC ranging between 397-1143 cells/mm^2, corresponding to a CEC loss of 57.7-85.3% (donor graft ECD ranged from 2400-2700 cells/mm^2).

Historical cohort – risk factors for IOL opacification following DMEK

A historic cohort of 232 DMEK eyes that were pseudophakic – standalone pseudophakic DMEK surgery, triple DMEK surgery, or staged CLE followed by DMEK surgery – was retrospectively analysed to estimate the rate of post-DMEK IOLop. Intraocular lens opacification at postoperative F-U slit-lamp examination

was documented in 21 eyes (9.05%). Five eyes (23.8%) had history of previous EK grafts, three of which two or more previous grafts. Six eyes (28.6%) had required rebubbling of the last DMEK graft; the mean number of rebubblings was 1.76 ± 1.09 (range = 1-5). In thirteen of these eyes, information on the IOL model was available, with two of the cases occurring with hydrophobic IOL models (15.4%), and the remainder (84.6%) with hydrophilic acrylic or "hybrid" IOL models (hydrophobic plus hydrophilic monomers).

In this cohort, 105 eyes had information on IOL material, and logistic regression analysis was performed to analyse risk factors for IOLop (n = 105). Variables that showed a p-value < 0.20 in the univariant analysis (Supplemental Table 1) were candidates for the multivariate analysis and included: indication for DMEK; IOL material; rebubbling; F-U time; axial length ≥ 23.27 mm; and ACD ≥ 3.36 mm. The final multivariate logistic regression model retained the variables "IOL material" and "number of rebubblings" as independent variables predictive of post-DMEK IOLop (Table 3). There was a very strong association between non-hydrophobic IOL models and IOLop (p = 0.0005) and each rebubbling was strongly associated with a 9.5-fold increase in the likelihood of post-DMEK IOLop (p = 0.0138). There was a non-statistically significant trend towards a higher likelihood of IOLop in eyes that underwent EK regrafting (p = 0.0805).

DISCUSSION

Intraocular lens opacification is an infrequent but likely underreported complication after DMEK. Based on our historic cohort analysis, we have estimated a 9.05% rate of IOLop, which is within the reported range derived from the limited literature available, where there is a widely variable incidence ranging between 0.44% and 12.9%.[2-4] The time between DMEK and the recognition of IOLop is highly variable, varying from few weeks to years after DMEK.[3,4] In our study, IOLop onset was detected as early as 2 weeks postoperatively and up to 10 months (44 weeks) after DMEK surgery. We have observed in our retrospective cohort that IOL materials with higher WC and higher number of rebubblings were strong, independent risk factors for post-DMEK IOLop, as well as a non-statistically significant trend towards postoperative IOLop in EK regraft

eyes. In our retrospective cohort, 84.6% of cases were “hybrid” or hydrophilic acrylic IOLs. Besides, in our cross-sectional study of eyes that underwent opacified IOL exchange, all eyes had hydrophilic acrylic or an “hybrid” IOL materials. Although IOL materials with high WC is likely the single most important independent risk factor for post-DMEK IOLop,[3,4] as is the case after Descemet stripping endothelial keratoplasty,[7-9] we have observed opacifications in eyes with hydrophobic IOLs as well, as have other authors.[3,4] The increased risk of post-EK IOLop in eyes needing rebubbling and regraft eyes likely reflects the “total” exposure of the IOLs to the endotamponade gas bubbles in the AC,[3,7]. Schrittenlocher *et al.* have also observed that patients with post-DMEK IOLop had higher rebubbling rates than patients without,[3] but Lorenzana-Blanco *et al.* did not observe an association between rebubbling and post-DMEK IOLop in their study.[4] Other risk factors for post-EK IOLop (both DSEK/DSAEK and DMEK) have been proposed inconsistently, including diabetes *mellitus*, glaucoma, and deep AC.[7]

Importantly, although many of the cases of IOL opacifications after DMEK are not visually significant either for their density of for their paracentral location,[9] our findings suggest that a relatively high proportion of cases may have a significant impact in BCVA and require explantation. Our estimate is in line with a recent report,[4] but is higher from another study where the authors only explanted one of fourteen opacified IOLs.[3] However, we consider that these are rough estimates, since it is possible that in some cases (in all studies) the IOL was not explanted despite BCVA decline; some studies have found a trend towards worse BCVA in affected eyes compared with unaffected DMEK eyes, even though IOL explantation was only considered in 7-20% of cases.[3,4] The decision of explanting an opacified IOL in this setting must carefully balance the degree of visual loss with the potential surgical complications that may lead to worse visual outcomes and/or pose risks for the DMEK graft.

To the best of our knowledge, ours is the first study to date to include detailed outcomes (both functional and anatomical, including EC loss and corneal thickness data) and safety of IOL exchange in the setting of post-DMEK IOLop, with a long F-U time after IOL exchange of nearly 4 years to support the relevance of our findings. It also reinforces the findings from the previous studies which are

remarkably limited.[3,4] In our study, IOL exchange was feasible and relatively safe in all four eyes. Following IOL exchange, we observed a quick visual recovery and a clinically significant improvement in final BCVA. This is in line with a recent study, where visual acuity improved from 1.75 to 0.60 logMAR following IOL exchange in DMEK eyes with opacified IOLs.[4] However, we highlight that IOL exchange is challenging in these cases, especially if patients have previous posterior capsulotomy. Perioperative complications include posterior capsular rupture and vitreous loss requiring anterior vitrectomy; zonular damage; postoperative CMO; corneal decompensation; OHT and glaucoma; uveitis; and suprachoroidal haemorrhage.[10-12] Although in our study all cases had clear corneas with functioning DMEK grafts at the study visit, these eyes may have accelerated EC loss (which can be due to iatrogenic trauma and due to perioperative inflammation or IOP increases), and this may pose the DMEK graft at risk for late endothelial graft failure in the medium-term. Intraocular lens explantation has resulted in DMEK graft failure in anecdotal reports.[2] The main limitation of our study is the small sample size of eyes that underwent IOL exchange. In addition, there was a high percentage of cases in the historical cohort where no information on the IOL model and material was available. This is because our institution has a broad, international referral basis for DMEK, and so data on cataract surgeries performed elsewhere was not available.

In conclusion, IOL opacification after DMEK surgery is a relatively infrequent complication, but up to one fifth of eyes may require IOL exchange or explantation due to significant impact in vision. Main risk factors for post-DMEK IOLop are IOL materials with high WC and rebubbling. Intraocular lens exchange is feasible, safe and effective in restoring good visual function. Although we observed no cases of graft failure in our study, these eyes may have an accelerated rate of EC loss, which may place the graft at risk for late endothelial graft failure.

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CAPTIONS

Figure 1 – Anterior segment photographs of opacified intraocular lenses (IOL) after Descemet's membrane endothelial keratoplasty (left), and during postoperative follow-up after IOL exchange retrieved from the patients' electronic medical records (middle). Specular microscopy measurements of postoperative endothelial cell count and pachymetry of the patients performed at the study visit.

Table 1– Cross-sectional study patients' characteristics before explantation of the opacified intraocular lens.

Legend: DMEK – Descemet's membrane endothelial keratoplasty; IOL – intraocular lens; IOLop – intraocular lens opacification; SGF – secondary graft failure; SF6 – sulphur hexafluoride; WC – water content; MF-IOL – multifocal intraocular lens; OHT – ocular hypertension; LASIK – laser in situ keratomileusis.

Table 2– Visual outcomes after intraocular lens exchange in eyes at the study visit.

Legend: BCVA – best-corrected visual acuity; DMEK – Descemet's membrane endothelial keratoplasty; IOLop – intraocular lens opacification; IOL – intraocular lens; F-U – follow-up.

Supplemental Table 1 - Univariant model for IOL opacification after DMEK.

** Not selected by AIC method*

*** These two variables are mutually exclusive*

**** "Rebubbling" and "No. of Rebubblings" are highly correlated (VIF factor→ 9954.57; 10 is the limit in generous studies). and "Rebubbling" was eliminated.*

Legend: OR – odds-ratio; 95%CI – 95% confidence interval; DMEK – Descemet's membrane endothelial keratoplasty; EK – endothelial keratoplasty; ACD – anterior chamber depth; FECD - Fuchs' endothelial corneal dystrophy.

Table 3 – Multivariate logistic regression model predictive of the risk of intraocular lens opacification after Descemet's membrane endothelial keratoplasty.

Legend: OR – odds-ratio; 95%CI – 95% confidence interval; IOL – intraocular lens; DMEK – Descemet's membrane endothelial keratoplasty.

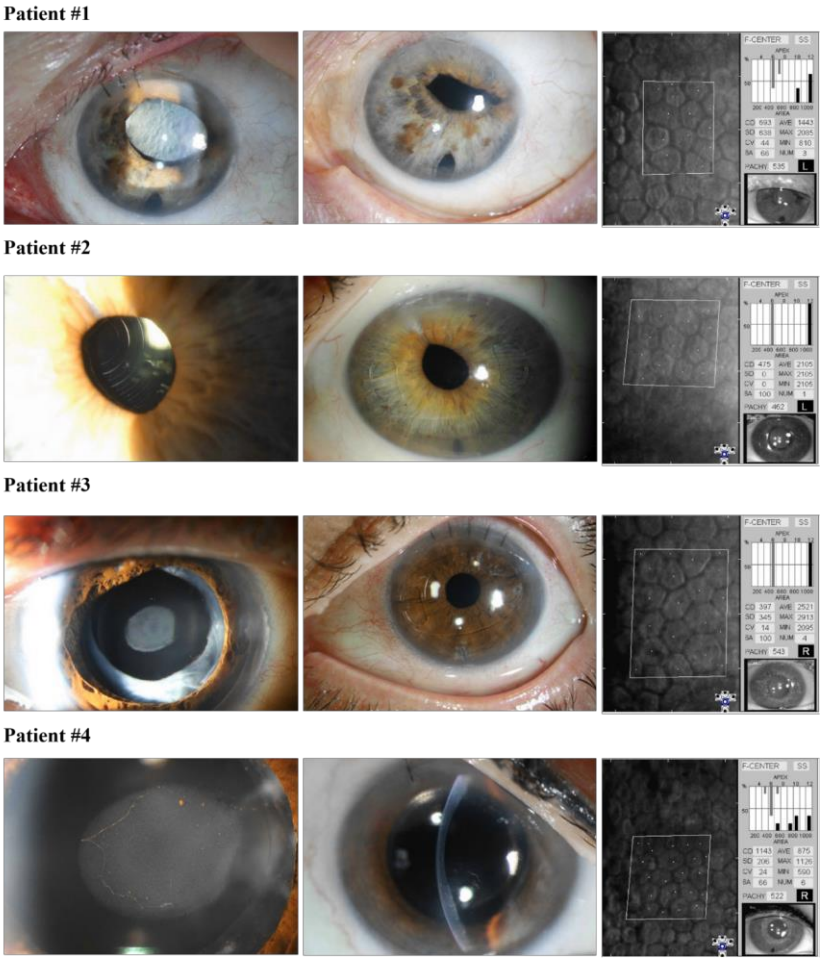


Figure 1 – Anterior segment photographs of opacified intraocular lenses (IOL) after Descemet's membrane endothelial keratoplasty (left), and during postoperative follow-up after IOL exchange retrieved from the patients' electronic medical records (middle). Specular microscopy measurements of postoperative endothelial cell count and pachymetry of the patients performed at the study visit.

Table 1 – Cross-sectional study patients' characteristics before explantation of the opacified intraocular lens.

Patients	Gender	Age at DMEK (years)	Laterality	Indication for DMEK	Previous ocular history	Redo DMEK	Type of DMEK surgery	Type of ocular endotamponade	Rebubbling after DMEK	Total No. Bubbles in the AC	IOL model	IOL material	Time between DMEK and IOLop detection (weeks)	Time to IOL exchange (months)
Patient #1	Female	76	Left	REPEAT DMEK	Cataract Surgery with Synechiolysis (2012) | Irregular Pupil | Glaucomatous Damage | Previous DMEK Graft Early SGF (M10) | No Diabetes	Yes	Graft Exchange	SF6 20%	No	2	AKREOS +23.50 D	26% WC Hydrophilic Acrylic	Onset 2 Weeks	12
Patient #2	Male	50	Left	PPBK	Complicated Cataract Surgery with Posterior capsule tear and decentred MF-IOL | OHT | No Diabetes	No	Standalone DMEK	SF6 20%	No	1	PHYSIOL MICRO F +21.50 D	25% WC Hydrophilic Acrylic	Onset 12 Weeks	11
Patient #3	Female	55	Right	FUCHS	Staged DMEK in Fellow Eye | No Diabetes	No	Staged DMEK surgery	SF6 20%	No	1	PRECIZON TORIC +30.25 SE (CYL 6.5)	Hybrid	Onset 44 Weeks	21
Patient #4	Female	58	Right	FUCHS	Amblyopic Eye | Myopic LASIK | No Diabetes	No	Staged DMEK surgery	SF6 20%	No	1	PRECIZON MONOFOCAL +26.00 D	Hybrid	Onset 30 Weeks	24

Legend: DMEK – Descemet's membrane endothelial keratoplasty; IOL – intraocular lens; IOLop – intraocular lens opacification; SGF – secondary graft failure; SF6 – sulphur hexafluoride; WC – water content; MF-IOL – multifocal intraocular lens; OHT – ocular hypertension; LASIK – laser in situ keratomileusis.

Table 2 – Visual outcomes after intraocular lens exchange in eyes at the study visit.

Patients	BCVA (LogMAR)				F-U after IOL exchange (months)	Residual manifest refraction at the study visit (D)
	Before DMEK	After DMEK, before significant IOLop	Before IOL exchange	At Study Visit		
Patient #1	0.80	0.00	0.18	0.00	40	-0.75 -0.75(150º)
Patient #2	0.40	0.18	0.30	0.00	99	+1.00 -1.25 (105º)
Patient #3	0.18	0.18	0.20	0.10	34	+2.25 -1.75 (140º)
Patient #4	0.40	0.20	0.45	0.18	50	-0.25

Legend: BCVA – best-corrected visual acuity; DMEK – Descemet's membrane endothelial keratoplasty; IOLop – intraocular lens opacification; IOL – intraocular lens; F-U – follow-up.

Table 3 – Multivariate logistic regression model predictive of the risk of intraocular lens opacification after Descemet's membrane endothelial keratoplasty.

Variable		OR	95%CI inf	95%CI sup	p
(N = 105)					
IOL Material	**Non-hydrophobic vs Hydrophobic**	**65.5**	**9.4211**	**1302.034**	**0.0005**
No. of Rebubblings		**9.51**	**1.7807**	**77.8558**	**0.0138**
Indication for DMEK	**Regraft vs Other**	5.47	0.8528	46.4731	0.0805

Legend: OR – odds-ratio; 95%CI – 95% confidence interval; IOL – intraocular lens; DMEK – Descemet's membrane endothelial keratoplasty.

Supplemental Table 1 – Univariant model for IOL opacification after DMEK.

Variable (N=105)	OR	95%CI lower	95%CI upper	p
Gender	1.86	0.53	8.75	0.3689
Age	0.99	0.94	1.05	0.7561
Age (best cut-off)	0		Inf	0.9905
Indication for DMEK	0		Inf	0.998
Indication for DMEK (FECD vs non-FECD)	1.36	0.38	4.44	0.6176
Indication for DMEK (Regraft vs Other)	3.8	1.02	13.32	**0.0382**
Diabetes	0		Inf	0.992
Glaucoma	1.45	0.07	10.06	0.744
Previous Grafts	0		Inf	0.9932
Previous EK Grafts (Yes)	1.82	0.37	6.95	0.4063
High Myopia	0.28	0.01	1.54	0.2313
Axial Length (mm)	0.95	0.7	1.19	0.6984
Axial Length Best_Cut (≥ 23.27 mm vs < 23.27 mm)	4.56	1.14	30.64	**0.0573**
ACD (mm)	2.02	0.69	5.95	**0.189***
ACD Best_Cut (≥ 3.36 mm vs < 3.36 mm)	2.65	0.81	8.98	**0.107**
IOL Material	6.17	0.26	74.46	**0.1605****
IOL Material (Others vs Hydrophobic)	22.61	5.48	154.82	**<0.0001****
Rebubbling (Yes)	2.96	0.72	10.77	**0.1081*****
No. of Rebubblings	4.56	1.57	14.06	**0.0055**
Total Number of Bubbles	1.63	0.9	2.85	**0.0873***
Total Number of Bubbles Best_Cut (≥1.5 vs < 1.5)	2.96	0.9	10.02	**0.0716**
Total Number of Bubbles (One Bubble vs Other)	0.34	0.1	1.11	**0.0716***
Follow-up Time	0.98	0.96	1	**0.0831**

** Not selected by AIC method*

*** These two variables are mutually exclusive*

**** "Rebubbling" and "No. of Rebubblings" are highly correlated (VIF factor→ 9954.57; 10 is the limit in generous studies). and "Rebubbling" was eliminated.*

Legend: OR – odds-ratio; 95%CI – 95% confidence interval; DMEK – Descemet's membrane endothelial keratoplasty; EK – endothelial keratoplasty; ACD – anterior chamber depth; FECD - Fuchs' endothelial corneal dystrophy.

Reference (List of Scientific Publications): XIV. Alonso-Reyes, H., Moura-Coelho, N., Lindez-Pérez, E., & Güell, J.L. (2024) *DMEK surgical strategy in aphakic and vitreous disease.* [Submitted].

Title: DMEK surgical strategy in aphakic and vitreous disease.

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Introduction

Descemet Membrane Endothelial Keratoplasty (DMEK) is a procedure that continues to be challenging with a steep learning curve, requiring additional considerations during surgery, particularly in patients who are aphakic and/or have undergone complete via pars plana vitrectomy. [1]

For a successful DMEK, optimal control of three main pillars is required: the anterior chamber (AC), the iris-lens diaphragm, and the vitreous. In aphakic eyes, the anatomy of the AC is affected by the lack of posterior support, resulting in a deeper AC and fluctuations of the iris-lens diaphragm. Additionally, achieving adequate tamponade of the AC with air or gas is often challenging, as fluctuations in the iris diaphragm and the intraocular lens (IOL), in those cases where a secondary implantation either in the anterior or posterior chamber has previously been made, led to recurrent globe collapse with subsequent migration of the tamponade agent into the vitreous cavity. [2]

Such challenging anatomy leads to issues with graft unfolding, especially in a deep AC where the graft tends to revert to its folded configuration. Although younger donor tissue is generally preferable, it tends to be more elastic, and not easy to handle during surgery, concerning the expansion of the graft within the AC. While grafts from younger donors exhibit the most pronounced tendency to roll inward, as the donor’s age increases this behavior significantly diminishes. In other words, the donor's age influences the unfolding of the lenticule, which is significantly more delayed and complex in the case of grafts from younger donors. This phenomenon can be explained by the age-related decline in elastin quantities and alterations in collagen structure, as well as an uptick in nonenzymatic glycosylation, leading to heightened stiffness in the Descemet membrane. [3]

Moreover, endothelial cell loss increases if the time required for unfolding is extended because of the amount of fluid introduced into the AC, and the maneuvers required for successful graft unrolling, besides the excessive fibrin and inflammatory cells that are released, further impeding successful unrolling because of their adherence to the donor lenticule. [3] These kind of complex eyes will have a higher

rate of postoperative complications including an increase in rebubbling rate and postoperative graft failure associated with a prolonged graft unfolding time. [4] Therefore, many surgeons prefer to proceed with DSAEK or full thickness keratoplasty in such patients group, as it is easier to manipulate a thicker tissue with fewer intraoperative complications and consequently, a lower graft failure rate. [5]

Table 1 lists all the previously published surgical strategies for a DMEK surgical approach in aphakic or vitrectomized patients.

“Small-Bubble technique” description

The surgical procedure starts, as standard[6], with the initial placement of two small incisions positioned at 3 o’clock 23G and 10 o´clock 20 G paracentesis. Air is introduced through the 3 o´clock 23 G paracentesis through an AC maintainer and a large descemetorhexis is performed under air with our reverse Sinskey hook through the 10 o´clock 20 G paracentesis.

We proceed with air-liquid exchange, inject miotic solution and perform an inferior iridectomy at 6 o´clock if it has not performed preoperatively. The donor graft is removed and stained with trypan blue, loaded into a cartridge preferably in the double roll form and then carefully injected in into the AC through a main incision 2.4 mm positioned at 11 o´clock. The proper alignment is subsequently verified by inspecting the outer edges of the graft and one suture is placed at the main incision. Subsequently, we introduce a small air bubble beneath the donor lenticule, aiding it to float at a significant distance to the posterior surface of the cornea (Figure 1). The donor lenticule is grasped by Güell Descemet’s Membrane Manipulation Forceps 22 Gauge[7] holding one free edge of the donor lenticule while the corneal surface is gently tapped (Figure 2), if necessary, from the center towards the periphery to complete the unfolding process. Once DM has been completely unfolded and properly centered, sulfur hexafluoride gas (SF6) 20% is injected under DM enlarging the “Small-Bubble”, fixating it on the posterior stroma using a special 30-gauge cannula with a hole in the superior side. If despite the pharmacological miosis, we

presume the bubble will move posteriorly, another bubble is injected into the anterior vitreous space.

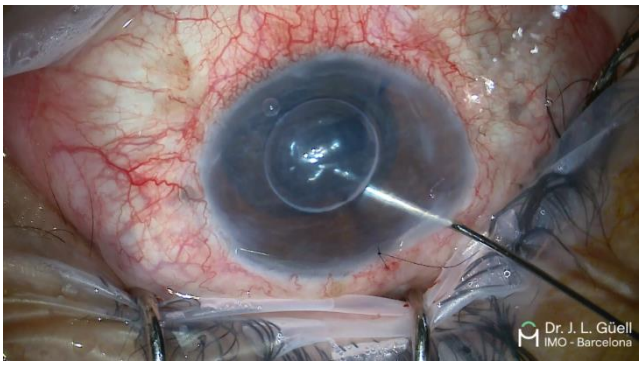


Figure 1. Small air bubble introduced beneath the donor lenticule, aiding it to float at a significant distance to the posterior surface of the cornea.

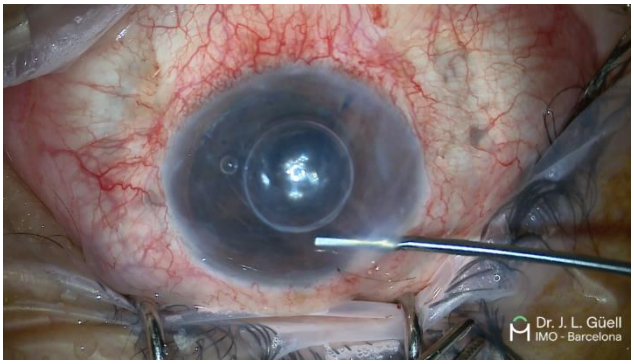


Figure 2. Donor lenticule grasped by Güell Descemet's Membrane Manipulation Forceps 22 Gauge holding one free edge.

Discussion

While successful DMEK procedures yield highly favorable clinical outcomes, graft failure remains a noteworthy concern, particularly in eyes that have undergone complete vitrectomy or are aphakic. Berguer et al. [8] reported a safety-Net Suture in three casas of aphakic patients using a continuous 10-0 polypropylene suture placed across the AC and then removed at the end of surgery. All cases were completed with no intraoperative posterior dislocation. Szurman et al. [9] showed similar outcomes in their case series using a temporary iris-lens diaphragm (inversely implanted contact lens) to assist the procedure in a phakic patients. On

the other hand, Karadag et al. [10] reported no intraoperative complications in their case series using the posterior half donor stroma manually dissected and temporarily place over the iris during the surgery.

Jyn Haur Woo et al. [11] described a hybrid DMEK technique using a bimanual pull-trough technique for DSAEK using the EndoGlide Ultrathin DSAEK donor insertion device performed in 37 complex eyes. Rootman et al. [12] employed a 23-gauge trocar inserted into the vitreous cavity connected to the infusion line for stabilize the anterior segment. Efdal Yoeruek et al. [13] describes a novel technique for improving DMEK in vitrecromized eyes using a temporary hydrophilic methacrylate sheet creating a doble anterior chamber and ensure that the donor graft does not dislocate into the vitreous cavity. Similar to this approach, Yusrah Shweikh et al. [14] published the use of an implantable collamer lens (ICL, STAAR Surgical) placed over the iris to provide a temporary intraoperative platform to facilitate graft unfolding and avoid posterior graft dislocation. Others, such as Johannes Gonnermann et al. [15] employed a posterior iris-claw aphakic IOL implantation with the same goal. Similar to our study Takahiko et al. [16] described a “Doble-bubble technique” characterized by 2 bubbles: 1 small above for the purpose of unfolding the graft and 1large beneath the graft to enable the fixation, although the unfolding time was relatively long (10.1±4.5 minutes), all surgeries were uneventful.

We think that our strategy approach is simple, highly reproducible once properly trained and requires a relatively short unfolding time, being indicated for patients with aphakia, those eyes previously vitrectomized and in some high myopic eye with deep anterior chambers and low scleral rigidity.

Table 1 – DMEK surgical techniques compilation in complex anterior segment disease

Autor (YEAR)	PAPPER	SURGICAL DESCRIPTION	RESULTS
Osvaldo Berger (2022)	Safety-Net Suture for Aphakic Descemet Membrane Endothelial Keratoplasty[8]	Continuous 10-0 polypropylene suture placed across the anterior chamber in a cat's-cradle pattern anterior to the trabecular meshwork (3 horizontals and 5 verticals). At the end of surgery, after air tamponade of the DMEK donor, the 10-0 polypropylene suture is removed.	All 3 cases were completed with no intraoperative posterior dislocation. A partial postoperative detachment in 1 case was successfully treated with repeat air tamponade. The corneas remain clear in early follow-up, 1 to 10 months after surgery.
Peter Szurman (2022)	Temporary iris-lens diaphragm to assist descemet membrane endothelial keratoplasty in aphakic patients[9]	Inversely implanted contact lens (standard fluorosilicone hydrogel *Air Optix*, Alcon) to create a temporary diaphragm to assist DMEK surgery in aphakic, partially aniridic and vitrectomized eyes.	Postoperative course was without pressure abnormalities, the anterior chamber remained deep. The cornea completely cleared within 3 weeks and remained clear after removal of the contact, after 7 months VA improved to 20/125. Required secondary procedure for contact lens explantation.
Remzi Karadag (2020)	Descemet's membrane endothelial keratoplasty in aphakic and vitrectomized eye[10]	The posterior half of the donor stroma is manually dissected and temporarily placed over the iris during the surgery for better anterior chamber stability and to form a barrier.	There were no intraoperative or postoperative complications during 1-month follow-up. Insertion of a temporary posterior stromal tissue as a barrier over the iris successfully provided AC stability and prevented posterior dislocation of the graft or air tamponade.
Jyh Haur Woo, Donald Tan (2020)	Hybrid Descemet Membrane Endothelial Keratoplasty (H-DMEK): results of a donor insertion pull-through technique using donor stroma as carrier[11]	Hybrid DMEK is performed using a bimanual pull-through technique using DSAEK-prepared donor stroma as carrier and the EndoGlide Ultrathin DSAEK donor insertion device.	85 eyes from 79 patients. DMEK was performed in 37 complex eyes. Four eyes required rebubbling and two cases of graft failure were observed. A BCVA of 20/25 or better was attained in 44.7% and 57.1% of eyes without pre-existing ocular pathology at 6 and 12 months, respectively.
D. S. Rootman (2019)	Long-term outcomes of descemet membrane endothelial keratoplasty in postvitrectomized eyes with the use of pars plana infusion[12]	A 23-gauge trocar was inserted into the vitreous cavity 3.0 mm from the limbus. A 23-gauge posterior infusion line was then connected to the trocar for the concept of stabilize the anterior segment during the procedure.	Five eyes had retinal complications including retinal detachment, retinoschisis, and cystoid macular edema. BCVA improved significantly to 20/200 at 24 months. Infusion may increase the risk of retinal complications.
Efdal Yoeruek (2018)	Novel technique for improving graft unfolding in vitrectomized eyes using a temporary diaphragm in descemet membrane endothelial keratoplasty[13]	Performing DMEK using a temporary hydrophilic methacrylate sheet creating a doble anterior chamber sustaining stability of the form of the globe in cases of previous complete vitrectomy.	All 7 patients had previously received complete pars plana vitrectomy and were pseudophakic. BCVA improved from 1.5±0.5 to 0.76±0.37 LogMAR. No complications were observed in any of the cases at the unfolding stage using this method.
Yusrah Shweikh (2018)	Phakic intraocular lens as a temporary barrier in aphakic Descemet's membrane endothelial keratoplasty[14]	Use of an implantable collamer lens (−8.00 D EVO+ Visian ICL, STAAR Surgical) placed over the iris to provide a temporary intraoperative platform, to facilitate graft unfolding and to avoid posterior graft dislocation in aphakic and vitrectomized eyes.	No further air injection was required and the graft remains attached and functioning well after surgery. The patient's visual acuity has improved to 6/9 with a +16 D sphere soft contact lens to correct aphakia.
Johannes Gonnermann (2014)	Posterior iris-claw aphakic intraocular lens implantation and Descemet membrane endothelial keratoplasty[15]	Patients without adequate capsular support and bullous keratopathy undergoing posterior iris-claw aphakic IOL implantation and subsequent DMEK.	The final BCVA improved significantly 0.33±0.31 logMAR. The mean endothelial cell loss was 24.8% over the follow-up. Complications included graft dislocation in four eyes; which could be easily reattached with a rebubbling procedure. No graft failures, no cases of pupillary block glaucoma and no IOL dislocations were encountered. Higher graft detachment rates.
Takahiko Hayashi (2017)	Double-Bubble Technique in Descemet Membrane Endothelial Keratoplasty for Vitrectomized Eyes: A Case Series[16]	Patients exhibiting endothelial dysfunction with aphakia, who underwent IOL-suture and pars plana vitrectomy. "Double-bubble technique" is characterized by 2 bubbles: 1 small above for the purpose of unfolding the graft and 1large beneath the graft to enable the fixation.	Although the unfolding time was relatively long (10.1±4.5 minutes), all surgeries were uneventful. Rebubbling was required in 1 eye. BCVA improved significantly in all eyes. There was no primary graft failure. All eyes underwent IOL suture previous DMEK procedure

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8.2.4. DESCRIPCIÓN DE LA TÉCNICA QUIRÚRGICA BÁSICA DE DMEK

La queratoplastía descemeto-endotelial (DMEK, del inglés D*escemet's membrane endothelial keratoplasty*) es una técnica de trasplantación corneal laminar, en la que se quita el complejo endotelio-membrana de Descemet (EDM, del inglés *Endothelial-Descemet's membrane*) del receptor y se trasplanta un lentículo donante de EDM, con un grosor uniforme de aproximadamente 10-15 µm.

La técnica fue originalmente descrita por Melles y colaboradores [1], e incluye la preparación del injerto DMEK y su inserción en un inyector, la preparación del receptor a través de la técnica de descemetorhexis, la introducción del lentículo donante en la cámara anterior (CA) y la aposición correcta del lentículo donante al estroma corneal posterior del receptor. Con la experiencia creciente en la cirugía DMEK, se desarrollaron técnicas alternativas para diferentes pasos de la cirugía, desde la preparación e inserción del injerto, a las técnicas de posicionamiento y aposición del injerto al estroma corneal posterior del receptor. Es interesante notar que hay una gran variabilidad en la práctica de DMEK entre los cirujanos de córnea entre diferentes países.[2]

Consideraciones sobre el tejido donante

La evaluación preoperatoria del tejido donante incluye la valoración de aspectos clínicos relacionados con el donante y con la preservación del tejido donante, la valoración macroscópica del tejido donante y la evaluación del endotelio corneal donante.

Existen algunos aspectos importantes a valorar de la historia clínica del donante de tejidos y que pueden tener influencia en la preparación y manipulación del injerto de DMEK. La edad del donante tiene influencia en la rigidez del tejido donante, y los complejos EDM de donantes con edades inferiores a 50 años tienen tendencia a enrollarse de forma más apretada, provocando mayor dificultad en desplegarse durante la cirugía, pudiendo implicar mayor manipulación del injerto. Greiner et al. han observado una mayor incidencia de rotura durante la preparación de injertos

DMEK en córneas donantes de individuos con diabetes *mellitus*.[3] Esto está en línea con los hallazgos del *Cornea Preservation Time Study* (CPTS), un ensayo clínico randomizado multicéntrico prospectivo con 1330 ojos intervenidos de DSAEK donde se observó que injertos laminares posteriores de donantes con diabetes *mellitus* se asocian a mayor tasa de desplazamiento de lentículo, a mayor riesgo de fracaso primario de injerto y a mayor tasa de pérdida de células endoteliales a los 3 años de seguimiento.[4,5] Finalmente, algunos estudios preliminares sugieren que el tiempo de preservación del tejido donante (PT, del inglés *preservation time*) no influye en los resultados clínicos de DMEK.[6] Sin embargo, en ojos intervenidos de DSAEK existe una tendencia en la que menores PT de tejido donantes se asocien a mejores resultados tras DSAEK (Moura-Coelho et al., comunicación personal, *World Ophthalmology Congress* 2020), a pesar de que PT inferiores a 12 días no parecen tener influencia significativa en los resultados de DSAEK (Moura-Coelho et al., comunicación personal, *World Ophthalmology Congress* 2020) en línea con los resultados del CPTS.[7] El *Cologne-Mecklenburg-Vorpommern DMEK Donor Study* (estudio COMEDOS) es un estudio prospectivo en curso que valorará las comorbilidades sistémicas y oculares de los donantes con los resultados de cirugía DMEK.[8]

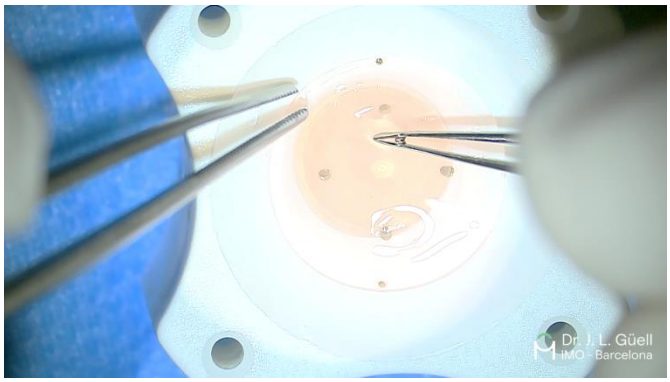
La evaluación de la córnea donante incluye la inspección macroscópica para valorar posibles lesiones corneales y para valorar la turbidez del medio de preservación. Además, se debería realizar una evaluación endotelial de la córnea donante, mediante microscopía especular. El contaje endotelial mínimo del injerto donante es variable según las regulaciones de cada país y de cada Banco de Tejidos. El Plan Nacional de Córneas 2016 recomienda una densidad celular ≥ 2500 células/mm^2 para las córneas donantes para trasplante tipo DMEK.[9] Además de la densidad celular, también es importante valorar aspectos morfológicos de las células endoteliales, como el porcentaje de células hexagonales y el tamaño celular, además de valorar la presencia de guttas, estrías endoteliales o precipitados queráticos. Es posible que injertos de DMEK obtenidos de córneas donantes cultivadas en medio de preservación tengan mejores resultados tengan mejores resultados que córneas frescas preservadas en medio Optisol-S, pero no es consensual.

Preparación del lentículo DMEK e inserción de injerto DMEK

La preparación del lentículo donante de DMEK puede ser realizado por el cirujano inmediatamente antes de la cirugía de DMEK, o puede ser preparado en un banco de tejidos (“preparado”) (Figura 1).

En la córnea donante no preparada en banco de tejidos, existen múltiples técnicas de separación del lentículo de DMEK, sin claras diferencias en la pérdida de células endoteliales entre ellas. La técnica de pelado manual originalmente descrita por Melles et al. y su “evolución” *SCUBA* (del inglés *submerged cornea using backgrounds away*) descrita por Giebel et al. son las técnicas más utilizadas. En la técnica SCUBA, la córnea donante es posicionada con el endotelio hacia arriba, la cara endotelial de la córnea es teñida con azul tripán al 0.06% durante 15-20 segundos para mejor visualización de los bordes del EDM, el complejo EDM es marcado en la periferia con un instrumento romo y la Descemet periférica externa al marcado inicial es extraída con pinza. Un instrumento romo o un gancho de Sinskey hace el marcado periférico, mientras con la otra mano el cirujano sujeta la córnea donante con un instrumento, por ejemplo, una pinza.

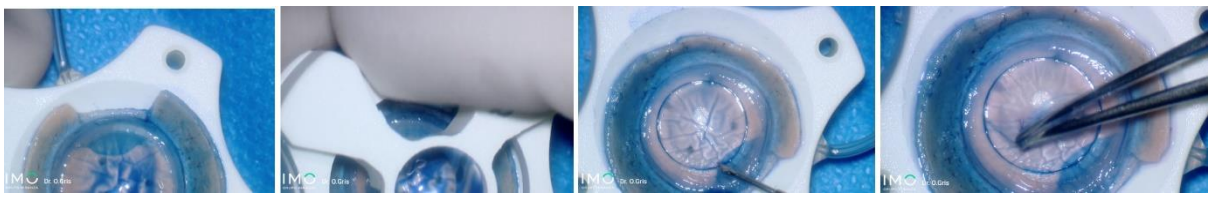
Figura 1: Pelado de complejo endotelio-membrana de Descemet de la córnea donante preparada en banco de tejidos, utilizando una pinza de DMEK (*Güell DMEK Forceps,* ASICO).



Existen algunas estrategias “clave” para asegurar el marcado correcto del complejo EDM: hacer la rotación de la córnea donante, tocar levemente el tejido para no

involucrar estroma posterior en el lentículo y para evitar desgarros y asegurarse de que el marcado es continuo. En seguida, bajo inmersión en BSS o en liquido de preservación, se eleva el borde periférico del endotelio con un gancho y se realiza el pelado del complejo EDM, cogiéndose el complejo EDM en el borde elevado con una pinza curva sin dientes y haciéndose un pelado de un 70-80% del complejo EDM. En esta fase, algunos cirujanos hacen un marcado en la cara estromal del lentículo a través de un agujero creado en la cara anterior de la córnea donante, que facilita la orientación correcta del injerto DMEK dentro del ojo del receptor. El complejo EDM es colocado en su posición original y se hace una trepanación parcial con el diámetro pretendido (habitualmente entre 7.5 u 8.0 mm). Se retira la Descemet periférica externa al borde de la trepanación y se finaliza el pelado del complejo EDM. Algunos cirujanos hacen un pequeño corte periférico con la forma de un triángulo escaleno tras la trepanación, que sirve para facilitar la orientación del injerto (Figura 2).

Figura 2: Separación del complejo endotelio-membrana de Descemet (EDM) en una córnea donante preparada en banco de tejidos. Tras la tinción del endotelio con azul tripán al 0.06% (2A), se realiza la trepanación parcial con el diámetro pretendido (2B). En seguida, se realiza un corte en la periferia del complejo EDM con la forma de un triángulo escaleno, lo que facilitará la orientación del injerto tras su inyección en la cámara anterior del paciente (2C). Finalmente, se finaliza el pelado del lentículo DMEK donante (2D).



Existen técnicas de disección pneumática del complejo EDM, descrita originalmente por Busin et al. y basadas en la técnica de *big bubble* de Anwar, donde se inyecta aire para separar la Descemet del estroma posterior.[10] Sin embargo, con esta técnica no siempre se logra obtener un injerto DMEK de diámetro superior a 7.0 mm.

La técnica de Muraine consiste en la hidrodisección del complejo EDM.[11] En esta técnica, la lámina de trepanación se rompe en un fragmento de 3-4 mm de largo. En seguida, se hace la trepanación de la Descemet en 330º con la córnea posicionada

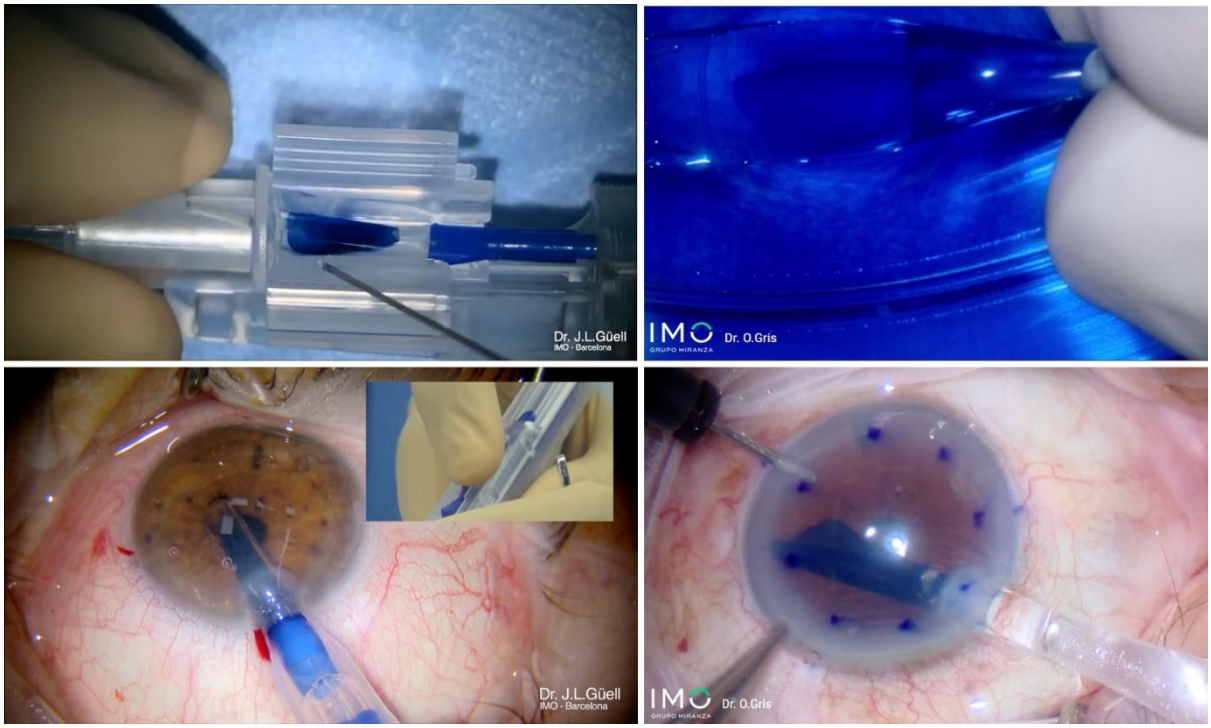
en una CA artificial con el endotelio hacia arriba. En seguida se cierra la CA artificial, dejando entrar aire en la CA artificial, lo que causa la inversión de la córnea con el endotelio proyectándose para arriba. El endotelio periférico puede posteriormente ser despegado con una espátula o con una pinza de Troutman, y se separa la Descemet con la pinza de Troutman pasando por debajo del flap creado. Posteriormente, se separa el complejo EDM del estroma posterior con BSS a través de una cánula de 27-gauge.

Recientemente, Tzamalis et al. describieron la técnica de "yogurt" para preparación de injerto de DMEK.[12] En esta técnica, se utiliza un trépano protegido (trépano de DMEK de Tzamalis) para trepanar parcialmente la córnea donante, dejando una pestaña de Descemet que se extende hasta la línea de Schwalbe, la que permite el pelado del complejo EDM con mayor facilidad técnica cogiendo esta pestaña con una pinza.

Es importante resaltar que existen múltiples variaciones de las técnicas de preparación de injerto de DMEK, descritas de modo exhaustivo en una revisión reciente por Singh y colaboradores.[13]

Tras prepararse el complejo EDM, este tiene la tendencia natural (fisiológica) a enrollarse sobre sí mismo, con el endotelio hacia fuera. Tras prepararse el injerto de DMEK, se carga el injerto en un inyector. Recomendamos hacer nueva tinción con azul tripán al 0.06% durante 1 a 3 minutos antes de cargarse el injerto DMEK en el inyector, para aumentar el contraste del injerto y mejorar su visualización una vez inyectado en la CA. Actualmente no disponemos de inyectores DMEK aprobados por la FDA. Existen múltiples inyectores, pero los dos tipos principales son la aspiración por un inyector de cristal (por ejemplo, el inyector de cristal de Geuder, *Geuder AG, Alemanía*) y el uso de inyectores de lentes intraoculares modificados (por ejemplo, *DMEK Güell injector 2.0, Medicel, Suiza*) (Figura 3). La selección del inyector es según la preferencia del cirujano. La principal ventaja de los inyectores de cristal es que la superficie es más suave que la de los inyectores de plástico, posiblemente causando menor traumatismo endotelial; la pérdida endotelial post-DMEK parece ser similar con ambos tipos de inyector.

Figura 3: Inyectores de DMEK – inyector de lente intraocular modificado tipo DMEK Güell injector 2.0, Medicel (izquierda) e inyector de cristal tipo Geuder, Geuder AG (derecha). La selección del inyector es según la preferencia del cirujano.



Recientemente surgieron técnicas de inserción de injerto DMEK con el endotelio hacia dentro (*"endothelium-in*"), que consisten en doblar el injerto en un *"triple fold"* con en endotelio hacia dentro, y cargando el injerto para un *DMEK EndoGlide* (*DMEK EndoGlide* , *Network Medical Products, Reino Unido*). Un meta-análisis reciente observó que las técnicas "*endothelium-in"* pueden disminuir la pérdida endotelial del injerto en comparación con las técnicas "*endothelium-out"*.[14]

PREPARACIÓN DEL RECEPTOR

La cirugía de DMEK se puede realizar bajo anestesía local y sedación, siendo excepcional el caso que necesite anestesía general (por ejemplo, pacientes con discapacidad mental, o pacientes muy jóvenes).

La preparación del ojo del receptor en la cirugía DMEK incluye la creación de incisiones quirúrgicas, la extracción del complejo EDM, la constricción pupilar y la creación de una iridotomia periférica (IP).

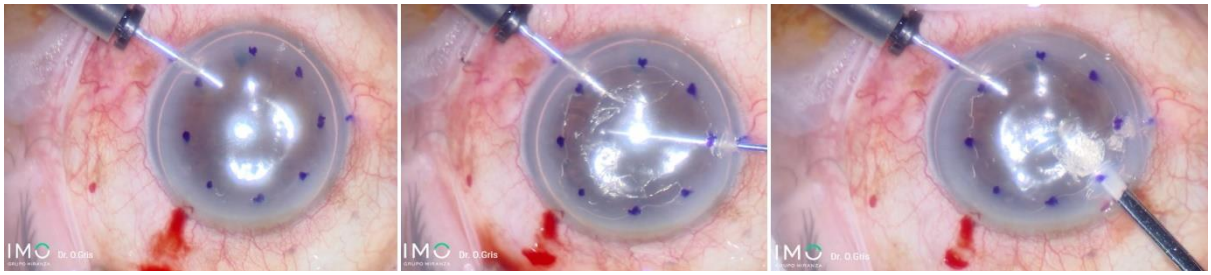
Incisiones quirúrgicas

La cirugía DMEK se puede realizar con abordaje superior o temporal, según la preferencia del cirujano y las características particulares del ojo del paciente. El número de paracentesis varía según la técnica y el cirujano. Nuestro grupo habitualmente crea una incisión superior entre 2.2 y 3.0-mm, una paracentesis para la descemetorhexis, una paracentesis para la infusión, y una incisión inferior de 23-gauge por donde realizamos la IP inferior. Otros cirujanos realizan la IP preoperatoriamente con láser o intraoperatoriamente con vitrectomo desde la incisión principal.

Descemetorhexis

La extracción del complejo EDM se realiza mediante la técnica de descemetorhexis, descrita originalmente por Melles y colaboradores.[15] La Descemet es separada del estroma posterior mecánicamente con un gancho de Sinskey inverso (*Price Endothelial Keratoplasty Hook, Moria SA, Francia*) (Figura 4). Para asegurarse de que no hay superposición del injerto DMEK a la Descemet del receptor, habitualmente se realiza una descemetorhexis con un diámetro mayor que el diámetro del injerto donante. Una vez separado el complejo EDM del estroma posterior, se trae el EDM hasta el centro del ojo y se extrae el EDM a través de la incisión principal, con una espátula roma, con movimientos suaves y atraumáticos para no lesionar el estroma posterior (Figura 4).

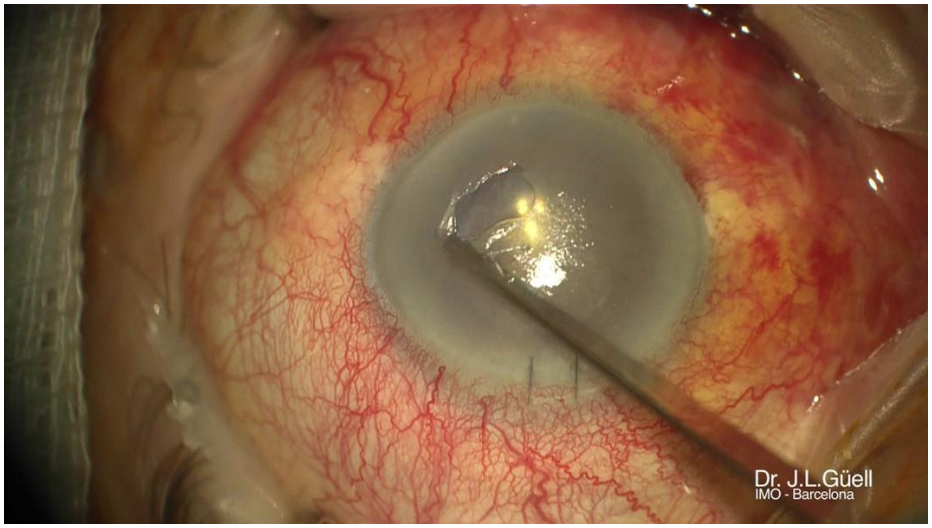
Figura 4: Descemetorhexis bajo infusión continua de aire (presión de infusión a 20 mmHg) a través de una cánula de infusión de 25-gauge conectada a una plataforma de vitrectomía (izquierda). Se puede hacer un marcado externo del diámetro pretendido; la descemetorhexis debe tener un diámetro mayor que el injerto donante. Se separa el complejo EDM del estroma posterior mecánicamente con un gancho de Sinskey inverso (centro); una vez separado, se extrae a través de la incisión principal, con una espátula roma para no lesionar el estroma posterior (derecha).



Existen algunas estrategias que facilitan la técnica quirúrgica y la realización de una descemetorhexis con un estroma posterior regular y sin *tags* o remanentes de Descemet. La desepitelización corneal es frecuentemente utilizada (Figura 5), ya que mejora la visualización del estroma posterior y de la CA (aunque haya cirujanos que prefieran no hacerlo). El marcado del diámetro de la descemetorhexis externo con un rotulador es opcional pero recomendable, sobre todo para cirujanos empezando la curva de aprendizaje de la cirugía de DMEK (Figura 4). Una CA estable facilita la descemetorhexis; se puede realizar bajo aire o bajo viscoelástico cohesivo, pero recomendamos habitualmente que se realice bajo aire ya que facilita la visualización del estroma posterior y de posibles remanentes de Descemet (Figura 4). Además, el uso de viscoelástico puede aumentar la incidencia de desprendimiento de injerto en el periodo postoperatorio. Utilizamos una cánula de infusión de 25-gauge y una presión de infusión de 20 mmHg con infusión continua de aire a través de una plataforma de vitrectomia.[16] Finalmente, resaltamos que la descemetorhexis es técnicamente más compleja en ojos con queratopatía bullosa pseudofaquica en comparación con ojos con distrofia endotelial de Fuchs.

Tras completarse la descemetorhexis y comprobar que no hay remanentes de EDM o irregularidades importantes del estroma posterior, se aspira el viscoelástico o el aire; cuándo utilizamos infusión de aire, procedemos al recambio de aire-fluido.

Figura 5: La desepitelización corneal puede facilitar la visualización del estroma posterior y del complejo endotelio-membrana de Descemet durante la descemetorhexis, además de facilitar la visualización del injerto donante en la cámara anterior.

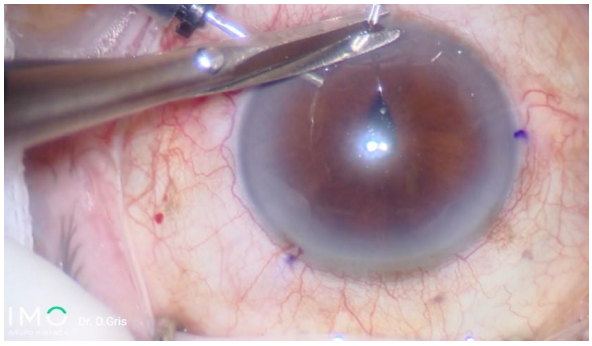


Constricción pupilar e iridotomia periferica

Tras realizarse la descemetorrhexis, es recomendable modular la pupila. Una pupila pequeña es útil en la cirugía de DMEK, ya que el iris protege el injerto donante del contacto con el cristalino o con la lente intraocular, y por otro lado la miosis protege el cristalino del efecto cataratogénico del gas de endotaponamiento en los casos de DMEK fáquicos. Además, cerrar la pupila también reduce el riesgo de migración del injerto DMEK para la cámara posterior en el momento de su inyección. La miosis farmacológica con acetilcolina intracameral es la técnica ideal; preconizamos no utilizar técnicas manuales de toque en el iris para aumentar el efecto miótico, ya que puede provocar hemorragia intraocular o inflamación con liberación de fibrina, aspectos que complican el desplegué y aposicionamiento del injerto DMEK y que además pueden causar complicaciones postoperatorias como el edema macular quístico (EMQ).

La constricción pupilar en la DMEK es recomendable, sin embargo, aumenta el riesgo de bloqueo pupilar postoperatorio. Por esta razón, se preconiza realizar IP inferior. La IP se puede crear intraoperatoriamente (Figura 6), o puede realizarse preoperatoriamente con el láser Nd:YAG. Los defensores de la creación de la IP preoperatoriamente lo hacen porque previene la aparición de hemorragia intraoperatoria y también porque puede disminuir la incidencia de EMQ postoperatorio (Capítulo 8.2.11.)

Figura 6: Iridectomia periférica (IP) inferior. La IP se puede realizar intraoperatoriamente o preoperatoriamente con el láser Nd:YAG.



Inserción del injerto en cámara anterior y orientación del injerto DMEK

Inyectar el injerto DMEK en la orientación correcta facilita el resto de la cirugía. La orientación correcta de un injerto DMEK *"endothelium-out"* es cuando las "alitas" del injerto miran hacia el estroma posterior del receptor. Según Veldman, los bordes sobrepuestos del lentículo DMEK se mueven en la misma dirección que la punta del inyector cuándo el injerto está correctamente orientado, y se mueven en la dirección contraria al inyector si el injerto está *upside-down* (técnica de Veldman-Venn para orientación de injerto DMEK).

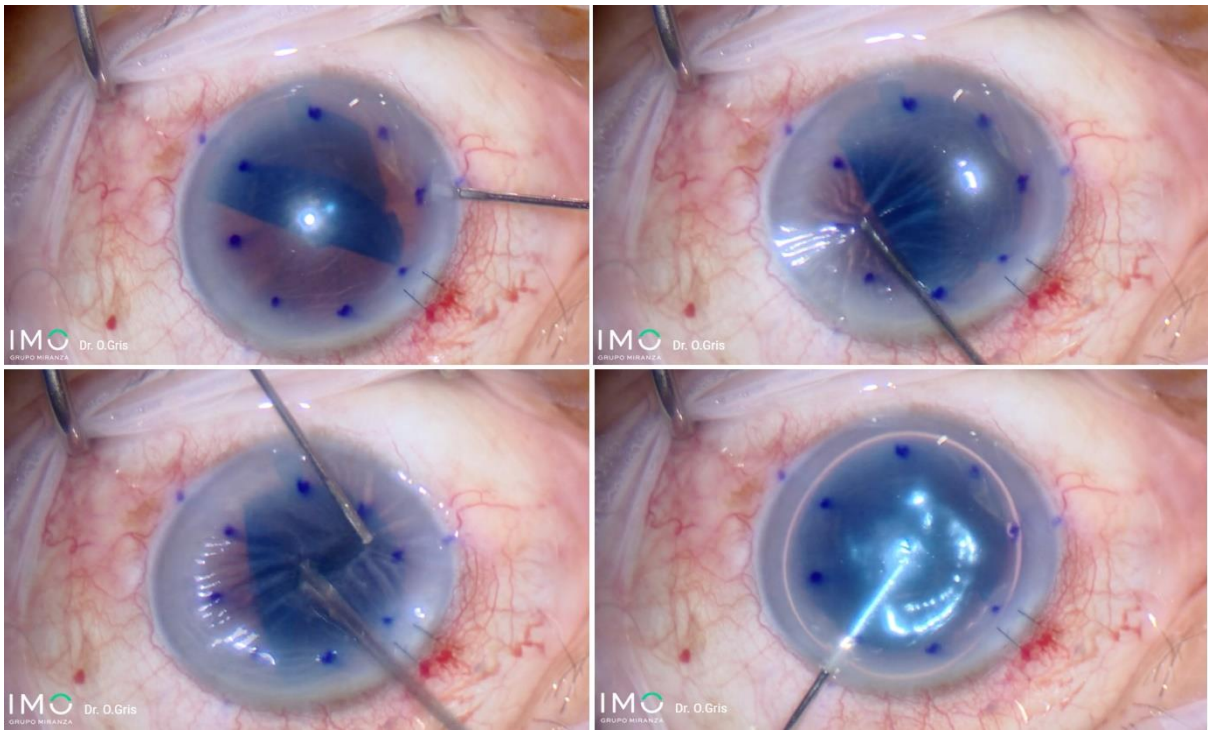
Tras confirmar la orientación correcta del injerto en el inyector, se baja la presión de infusión de BSS en la CA a 5 mmHg para preparar la inyección del injerto DMEK [16], cerrándose la infusión en el momento de inyectar el injerto DMEK (Figura 3). Recomendamos que en el momento de entrada del lentículo DMEK en la CA que se

retire la infusión, una vez que una CA poco amplia (pero no colapsada) facilita la manipulación y despliegue del injerto DMEK, además de que una presión de infusión inadecuada puede conducir a la expulsión del injerto DMEK en el momento que se retira el inyector de la incisión principal.

Tras la inyección del lentículo DMEK en la CA, recomendamos que se cierre la incisión principal con sutura (por ejemplo, monofilamento 10-0), para prevenir la expulsión de injerto durante su manipulación y despliegue.

Una vez el injerto DMEK está en la CA, hay que confirmar la orientación correcta del mismo, ya que este puede cambiar su orientación en el momento de la inyección. Hay múltiples técnicas para valorar la orientación. Se puede expandir la CA con BSS mientras se hacen maniobras de *tapping* de la superficie ocular, para crear pequeñas olas de fluido y facilitar la visualización de la orientación del injerto. El signo de Moutsouris es una estratégia sencilla para confirmar la orientación del injerto; con una cánula metida anteriormente al injerto, si el injerto está correctamente orientado entonces la cánula al moverse se pondrá de color azul; si el injerto está *upside-down*, la cánula sigue con su color gris original. Otras técnicas de orientación del injerto incluyen la utilización de luz en hendidura o de endoiluminación. Hay autores que consideran la tomografía de coherencia óptica intraoperatoria (iOCT) el *gold standard* para observar la orientación del lentículo DMEK.[17] Si se hizo algún marcado en el injerto donante (por ejemplo, el marcado en la cara estromal del lentículo o el corte periférico del complejo EDM con la forma de un triángulo escaleno), no hay riesgo de equivocarse en la orientación (Figura 7).

Figura 7: Despliegue y centramiento del injerto DMEK. La inyección de pequeñas cuantidades de BSS facilitan el despliegue del injerto (7A). Las técnicas de *tapping* en la superficie corneal con cánula (7B y 7C) permiten el despliegue y centramiento del injerto DMEK minimizando la pérdida de células endoteliales del injerto. Una vez asegurado el posicionamiento y orientación correctos del injerto DMEK, se inyecta SF6 al 20% en la cámara anterior, para aposicionar el injerto DMEK al estroma corneal posterior del receptor (7D).

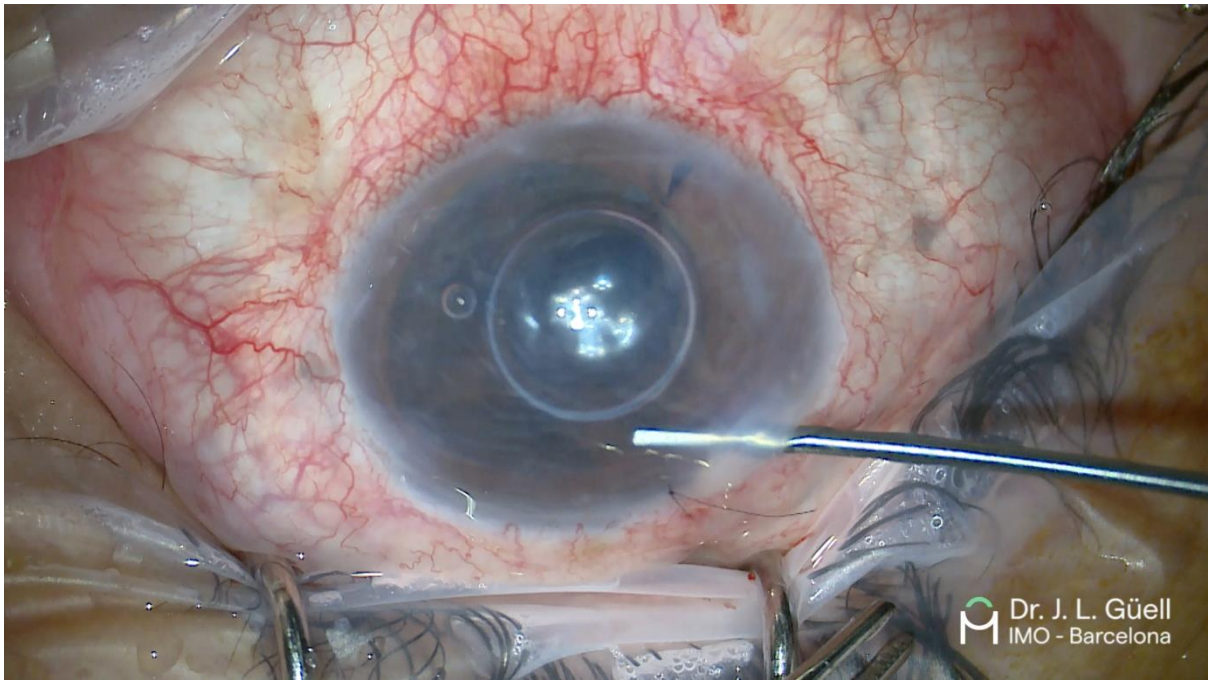


Si encontramos el injerto incorrectamente orientado, una estrategia frecuentemente utilizada para orientarlo correctamente consiste en inyectar pequeñas cuantidades de BSS a través de la paracentesis, para crear olas de fluido internas que causan la rotación del injerto.

Tras confirmar la orientación correcta del injerto DMEK en la CA, existen múltiples técnicas para desplegar y centrar el lentículo DMEK (Figuras 7 y 8). Típicamente se utilizan técnicas de *tapping* en la superficie ocular externa con cánula (técnicas *no-touch*). Recomendamos una CA poco profunda o incluso colapsada en el momento de desplegar y centrar el injerto DMEK, ya que facilita las maniobras. Se puede utilizar BSS y burbuja de aire para ayudar al despliegue del injerto, pero cuidadosamente para evitar una pérdida de células endoteliales yatrogenica aumentada. Yoeruek y colaboradores describieron originalmente la técnica de

tapping de superficie, utilizando la indentación ecuatorial digital y un instrumento para ir tapeando la superficie de la córnea y desplegando y posicionando el injerto.[18] Dirisamer y colaboradores han refinado esta técnica, utilizando dos cánulas, utilizando una cánula que va desplegando el injerto DMEK y una segunda cánula en la periferia de la córnea que presiona la córnea receptora contra el iris y estabiliza el borde ya desplegado del injerto DMEK.[19] Nuestro grupo ha descrito originalmente la técnica bimanual para inyectar y posicionar el injerto DMEK con BSS, utilizando una cánula de Gills conectada a un sistema de irrigación-aspiración automático, con bajo flujo de irrigación unido a técnicas de *tapping* corneal.[16] Recientemente, Vasquez-Perez ha descrito la técnica de *spinning*: posicionando el lentículo DMEK perpendicular a una paracentesis, con una cánula de Rycroft de 30-gauge se inyectan pequeñas cuantidades de BSS que provocan la rotación del injerto sobre su eje y su desplegué como resultado de las fuerzas centrifugas. Finalmente, en casos complejos y/o de difícil despliegue y centramiento del injerto DMEK, se pueden utilizar técnicas de manipulación directa del injerto con instrumentos que sean atraumáticos para el lentículo, por ejemplo, la pinza de manipulación de lentículo DMEK de Güell (*Güell Descemet's Membrane Forceps,* Duckworth & Kent). (Figura 8)

Figura 8: El centramiento del injerto DMEK puede realizarse con auxílio de manipuladores directos del injerto (*Güell Descemet's Membrane Forceps,* Duckworth & Kent), técnica especialmente útil en ojos ojos complejos como ojos afáquicos o ojos vitrectomizados; resaltamos la importancia de maniobras atraumáticas para el injerto DMEK para minimizar la pérdida de células endoteliales.



El despliegue y el centramiento con maniobras minimamente traumáticas es fundamental para prevenir la pérdida endotelial iatrogénica que puede llevar al fracaso primario de injerto y que tiene impacto negativo en el pronóstico a largo plazo de la DMEK.[20] Se va centrando el injerto durante el despliegue y tras estar completamente desplegado, y puede ser necesario recentrarlo varias veces antes de procederse al endotaponamiento, con técnicas de *no-touch*, técnicas con burbuja de aire o con BSS. Tapear la superficie de la córnea hace que el injerto se mueva en la dirección pretendida, y la indentación escleral suave con una cánula resulta en el movimiento del injerto en su dirección (por ejemplo, un injerto descentrado nasalmente se puede recentrar utilizando la técnica de indentación escleral temporal). Se pretende que el injerto esté centrado en la zona de la descemetorhexis y, como hemos comentado anteriormente, es ideal que exista una pequeña área de separación entre el injerto donante y la Descemet periférica del receptor.

Aposición de injerto DMEK al estroma posterior y endotaponamiento

Tras desplegar completamente el injerto y centrarlo en la orientación correcta, es necesario inyectar una burbuja de aire o gas para aposicionar el injerto donante contra el estroma corneal posterior del receptor (endotaponamiento). La burbuja de gas tiene como objetivo mantener la aposición del injerto mientras se establece la función de bomba endotelial del injerto (Figura 7). Se puede utilizar aire al 100% o SF6 al 20% o menor, como ha descrito originalmente nuestro grupo.[21] Un meta-análisis reciente de 1195 DMEKs ha comprobado que el endotaponamiento con SF6 al 20% se asocia a un menor riesgo de *rebubbling*, sin afectar las células endoteliales y sin aumentar el riesgo de bloqueo pupilar.[22] Un abordaje frecuente entre cirujanos corneales consiste en llenar completamente la CA de gas durante algunos minutos y seguidamente retirar algún volumen de gas, dejando aproximadamente 80-90% de la CA llena por gas; el aspecto más importante es asegurarse de que el gas no obstruya la IP, para prevenir el bloqueo pupilar. Finalmente, es importante asegurarse que el ojo presenta un tono adecuado al final de la cirugía, aunque también existan diferentes opiniones al respeto.

En el final del procedimiento, se puede inyectar cefuroxima intracameral como profilaxis de la endoftalmitis postoperatoria, que ha demostrado ser segura para el injerto DMEK, sin pérdida endotelial acelerada ni aumento de riesgo de *re-bubbling.*[23] En casos de riesgo inmunológico más elevado (por ejemplo, ojos con trasplantes corneales previos), se puede inyectar un corticoide subconjuntival al final del procedimiento como profilaxis del rechazo inmunológico de injerto, aunque para nosotros es un paso estándar en cualquier caso de trasplante corneal.

POSICIONAMIENTO POSTOPERATORIO

El posicionamiento postoperatorio es considerado fundamental para disminuir el riesgo de desprendimiento de injerto y necesidad de *rebubbling* post-DMEK; un meta-análisis concluyó que un tiempo de supino postoperatorio más prolongado se asocia a 58% menor probabilidad de *rebubbling*.[22] Nuestro grupo típicamente posiciona el paciente en supino durante 45-60 minutos en la unidad postoperatoria, y luego durante la primera semana recomendamos adoptar diferentes posiciones de

la cabeza para aumentar el contacto del gas con toda la superficie del injerto.[16] Sin embargo, es curioso notar que algunos autores han observado que el posicionamiento postoperatorio puede no influenciar el riesgo de desprendimiento de injerto con impacto clínico.[24,25]

CONCLUSIONES

La técnica de DMEK han evolucionado desde la primera descripción por Melles y colaboradores. Con la experiencia creciente a nivel mundial, han aparecido modificaciones con el objetivo de hacer técnicas con menor curva de aprendizaje, con menor pérdida endotelial y con menores tasas de desprendimiento de injerto y *re-bubbling*. Hay una adopción progresiva del uso de córneas preparadas en banco de tejidos, una vez que estandariza la preparación de injertos DMEK y disminuye el riesgo de complicaciones relacionadas con la preparación del injerto por el cirujano. En el futuro, es probable que surjan injertos de DMEK pre-cargados en inyectores, que minimizarán la pérdida endotelial relacionada con la inserción del injerto en el inyector. Finalmente, las técnicas de manipulación y aposición del injerto en la CA del receptor van siendo mejoradas, y con mayor experiencia quirúrgica se observa menor manipulación del injerto y menores tasas de descentramiento y desprendimiento de injerto post-DMEK.

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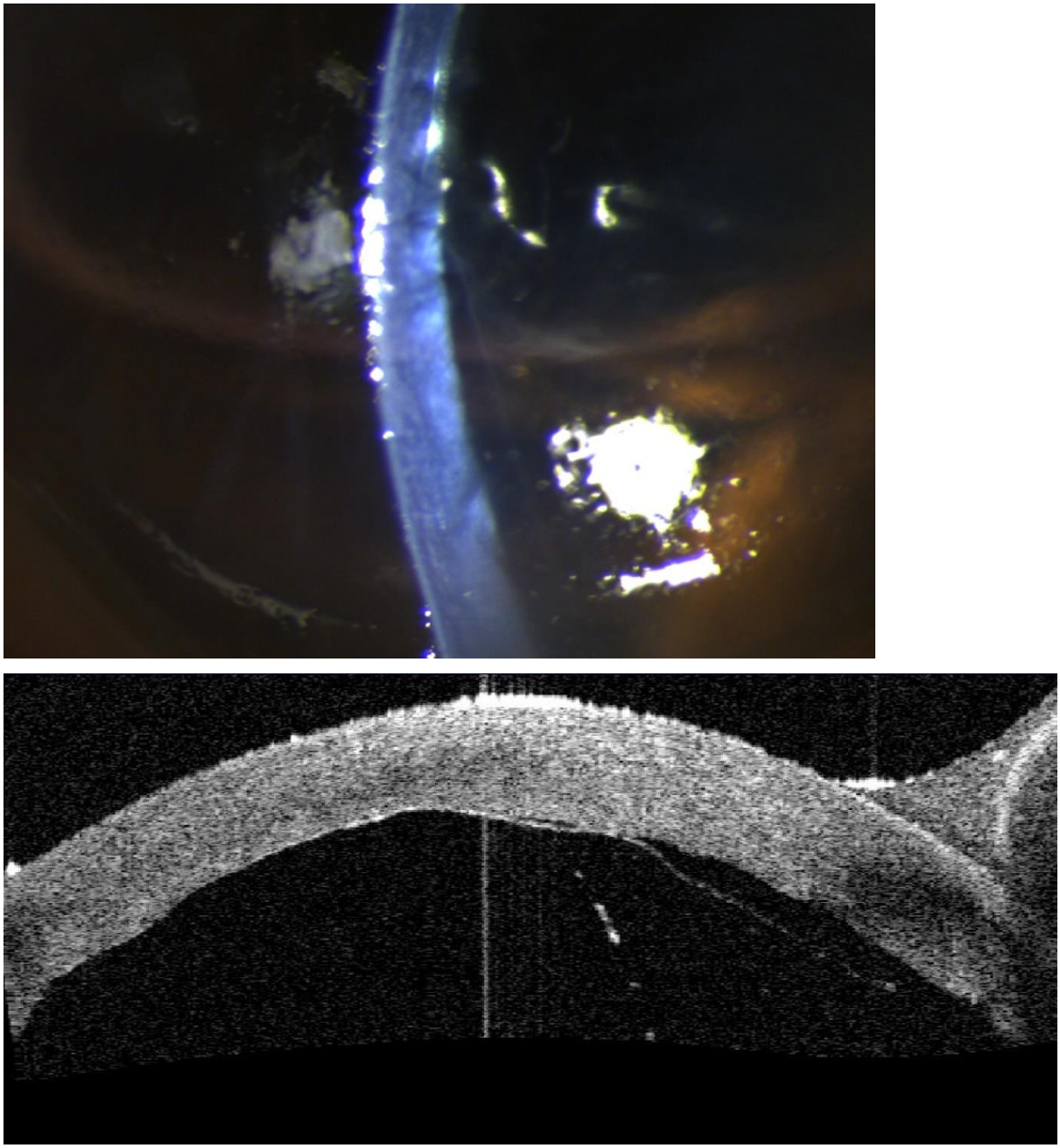
8.2.11 COMPLICACIONES POSTOPERATORIAS EN DMEK

La queratoplastia laminar posterior es actualmente el "*gold standard"* del tratamiento de las enfermedades del endotelio corneal, particularmente la queratoplastia descemeto-endotelial (DMEK, del inglés D*escemet's membrane endotelial keratoplasty*) atendiendo a la rápida recuperación visual, buenos resultados visuales y refractivos y bajo riesgo de rechazo inmunológico. Sin embargo, y a pesar de los avances continuados en la técnica quirúrgica y la expansión de las indicaciones para DMEK, el número creciente de DMEK realizadas cada año y los casos de DMEK con seguimientos a largo plazo hacen que sea importante reconocer las posibles complicaciones intra- y post-operatorias de DMEK para asegurar su prevención y manejo.

Desprendimiento del lentículo donante

El desprendimiento del lentículo donante (GD, del inglés "*graft detachment"*) es la complicación postoperatoria de DMEK más frecuente, con una frecuencia variable que va desde un 2.5% hasta un 40% de todas las DMEKs.[1-6] Sin embargo, la mayor parte de los GD no tienen impacto clínico, ya que en muchos casos el desprendimiento es parcial y se resuelve espontáneamente con el tiempo. En los casos extremos de GD con desprendimiento completo de injerto, el injerto puede fallar primariamente, y en ojos aniridicos o afáquicos existe el riesgo de migración posterior del injerto. En los casos donde el GD parcial tiene impacto clínico (Figura 1), está indicada la reinyección de gas ("*re-bubbling"*) para asegurar la aposición del lentículo donante al estroma posterior del huésped. Típicamente, se considera el *re-bubbling* en casos de GD persistente o progresivo y/o con impacto en la agudeza visual (AV), con edema corneal persistente que afecta el eje visual; u ojos con GD > 20% y con afectación paracentral; algunos autores consideran *re-bubbling* si el GD tiene más de 2 horas de reloj con edema corneal.

Figura 1: Fotografia de segmento anterior (1A) y tomografía de coherencia óptica de segmento anterior (1B) de desprendimiento de injerto DMEK con impacto clínico, con extensión al eje visual y edema corneal.



Existen múltiples factores de riesgo asociados a una mayor incidencia de *re-bubbling*: ojos con injertos corneales penetrantes o laminares posteriores previos, ojos complejos (por ejemplo, ojos afáquicos, ojos intervenidos de glaucoma u ojos vitrectomizados), cirugía complicada, corta duración del endotaponamiento con gas, endotaponamiento con aire en comparación con SF6, presión intraocular (PIO)

inferior a 10 mmHg durante las primeras semanas postoperatorias.[2] Un meta-análisis reciente de 1195 ojos de DMEK concluyó que el endotaponamiento con SF6 al 20% y tiempo de supino postoperatorio más prolongado se asocia a 58% menor probabilidad de *re-bubbling*.[7] Sin embargo, es curioso notar que algunos autores han observado que el posicionamiento postoperatorio puede no influenciar el riesgo de GD clínicamente significativo.[8-9] La variación del grosor central corneal en el primer día post-DMEK también puede tener valor predictivo de *re-bubbling*, ya que la disminución del grosor se asocia a una reducción de 5.7 veces el riesgo de *re-bubbling.*[6] Es probable que existan factores intrínsecos del huésped que aumenten el riesgo de *re-bubbling*, ya que en el *Cologne re-bubbling study* (un estudio multicéntrico de 1541 DMEKs) se observó que un 58% de pacientes con historia de *re-bubbling* en el primer ojo tuvieron GD con necesidad de *re-bubbling* en el segundo ojo, en comparación con la tasa global de 32% [3]; de hecho, la edad avanzada del huésped parece ser un factor de riesgo independiente para *re-bubbling* [10], y ojos con alteraciones ultra-estructurales de la membrana de Descemet parecen tener mayor riesgo de GD y de fracaso de injerto DMEK en comparación con ojos con Descemet no anómalas.[11] Otros factores que pueden estar asociados a GD pero que no son consensuales incluyen el descentramiento del injerto, descemetorhexis pequeña, edad avanzada del huésped y edad del donante más baja. A pesar de que la cirugía triple se asocia a mayor riesgo de *re-bubbling* en la mayor parte de los estudios [12], esto ha sido contestado como no significativo por otros autores.[13] Finalmente, es probable que la experiencia del cirujano tenga alguna asociación con el riesgo de GD y *re-bubbling*.

La tasa de éxito del *re-bubbling* en ojos con GD tras DMEK, donde se observa aposición correcta del lentículo donante al estroma posterior del huésped y con disminución del edema corneal, es aproximadamente de 70-80%.[1,10] *Re-bubbling*s tardíos (realizados > de 1 mes tras DMEK) tienen peor tasa de éxito [14], ya que ocurre un aumento de la rigidez del injerto donante con el tiempo. La influencia del *re-bubbling* en la pérdida adicional de células endoteliales no está clara [3,10], y tampoco que los ojos que necesitan *re-bubbling* tengan peor pronóstico del injerto DMEK en comparación con ojos sin necesidad de *re-bubbling*.[3]

BLOQUEO PUPILAR

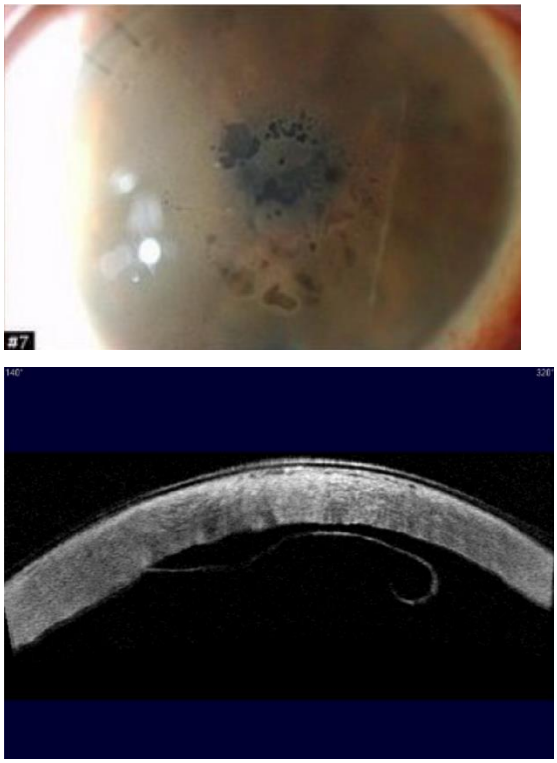
El endotaponamiento con aire o gas para asegurar la aposición del lentículo de DMEK puede provocar un fenómeno de bloqueo pupilar, una complicación potencialmente amenazadora de visión. Las tasas de bloqueo pupilar tras DMEK varían entre un 0% y un 15% en las series publicadas [15], siendo los principales factores de riesgo prevenibles la presencia de una burbuja de gas llenando el 100% de la cámara anterior al final del procedimiento y la ausencia de iridotomia. Sin embargo, actualmente la tasa de bloqueo pupilar ha disminuido hasta casi el 0% con la adopción generalizada de iridotomia periférica inferior. Esta puede ser realizada con el láser preoperatoriamente, o realizada intraoperatoriamente durante la cirugía de DMEK. Algunos autores defienden que la realización de iridotomia preoperatoria disminuye el riesgo de hemorragia intraoperatoria, de *re-bubbling* y también el riesgo de edema macular quístico (EMQ) postoperatorio. Sin embargo, y a pesar de la realización de iridotomia, el riesgo de bloqueo pupilar no es nulo, y se recomienda comprobar que la iridotomia esté permeable (sin superposición de gas) una hora tras el final de la cirugía (con el paciente sentado) y que el ojo tenga una PIO inferior a 30 mmHg; en estos casos, se recomienda disminuir la dimensión de la burbuja de aire.

FRACASO PRIMARIO Y FRACASO SECUNDARIO DE INJERTO DMEK

El fracaso primario de injerto DMEK (PGF, del inglés "*primary graft failure"*) se define habitualmente como la persistencia de edema corneal 2-3 meses después de la cirugía, a pesar de una perfecta aposición y orientación del injerto donante al estroma posterior del huésped. La incidencia media de PGF tras DMEK es del 1.9%, variando entre el 0% y el 12.5% según los autores.[16] Sin embargo, la tasa de PGF tras DMEK parece ser favorable en comparación con la tasa de PGF tras DSEK/DSAEK.[17] Los principales factores de riesgo para PGF parecen ser la presencia de complicaciones intraoperatorias, un tiempo de cirugía prolongado y la experiencia quirúrgica del cirujano, con un gran estudio neerlandés a nivel nacional observando que las cirugías realizadas antes del 2016 tenían un mayor riesgo de PGF que las subsequentes.[10] Una causa de PGF en las series iniciales de DMEK era la presencia de un injerto *upside-down* (Figura 2); sin embargo, con el

perfeccionamiento de la técnica quirúrgica, esta complicación es prácticamente inexistente.

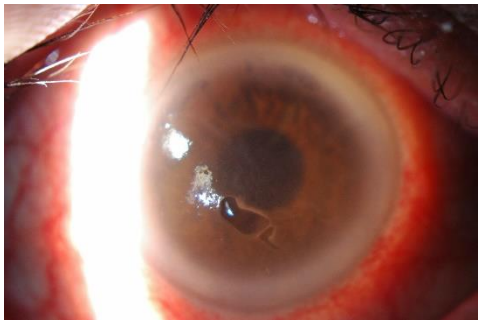
Figura 2: Injerto DMEK reverso (*"upside-down*"). Edema corneal persistente tras la cirugía de DMEK (2A), observándose injerto reverso en la tomografía de coherencia óptica de segmento anterior (2B).

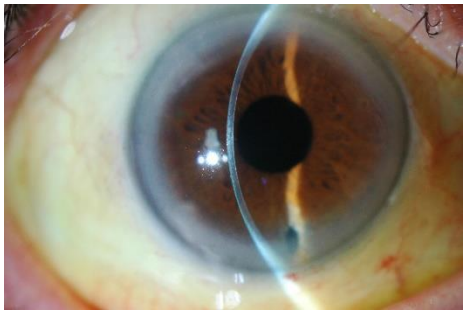


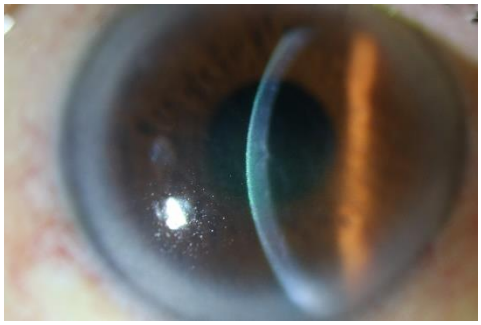
El fracaso secundario de injerto DMEK (SGF, del inglés "*secondary graft failure"*) se define como la descompensación corneal en un ojo intervenido de DMEK tras un período de trasparencia corneal (Figura 3). El SGF puede ser resultante de la pérdida progresiva de células endoteliales del injerto (LEGF, del inglés "*late endotelial graft failure"*) o tener una causa, como por ejemplo el rechazo inmunológico, infección, hipertensión ocular (HTO) persistente o glaucoma (que ocurre en hasta un 15% de los pacientes operados de DMEK, sobre todo en pacientes con glaucoma previo a la cirugía de DMEK, y que se asocia a un peor pronóstico de DMEK), o iatrogénico en ojos intervenidos tras la cirugía de DMEK. La incidencia media de SGF es de un 2.2% [16], pero es altamente variable según los estudios y dependiente del tiempo de seguimiento post-DMEK. En algunos casos, se observa un corto período de trasparencia corneal tras la cirugía seguido de

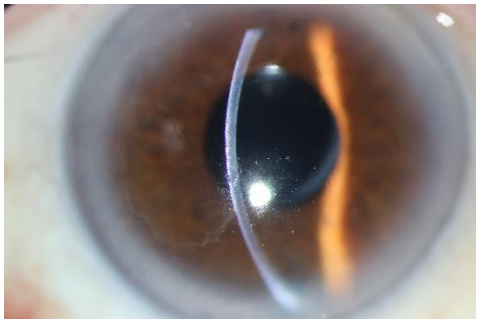
descompensación corneal ("*early graft failure*"), que probablemente resulta de una pérdida endotelial importante en los primeros meses tras la cirugía DMEK.

Figura 3: Fracaso secundario de injerto DMEK. En este caso de queratopatia bullosa pseudofáquica (Figura 3A), se realizó DMEK primaria, con rápida resolución del edema corneal y recuperación de la trasparencia corneal (Figura 3B). A los 3 años de seguimiento, se observó descompensación corneal con necesidad de re-transplante (Figura 3C). Tras la re-DMEK, se observó rápida recuperación de la agudeza visual y de la trasparencia corneal (Figura 3D).









La probabilidad de supervivencia de un injerto primario de DMEK está íntimamente relacionada con el tiempo de seguimiento postoperatorio y con la pérdida de células endoteliales postoperatoria.[18] En los primeros 6 meses post-DMEK, se observa una pérdida endotelial media de un 24-37%, similar a la pérdida endotelial tras DSAEK y mayor que la pérdida endotelial tras QPP. Sin embargo, después de los primeros 6-12 meses de cirugía, la pérdida endotelial crónica a medio y a largo plazo de la DMEK asume un perfil lineal y con una pérdida endotelial más lenta en comparación con los ojos operados de QPP, con pérdidas variables entre 36-43% a los 3 años de seguimiento, de 48-55% a los 5 años de seguimiento, y de 71% en ojos con 10 años de seguimiento.[19] La pérdida endotelial crónica a partir de los 3-5 años de seguimiento es similar a la pérdida endotelial tras DSAEK y favorable en comparación con la tasa de pérdida endotelial tras queratoplastia penetrante en el *Cornea Donor Study*.[19,20]

La probabilidad acumulativa de supervivencia de injerto DMEK es de un 83-95% a los 5 años de seguimiento y de un 79% en ojos con 10 años de seguimiento.[19,21]

Se estima que un 7-10% de las queratoplastias tipo DMEK realizadas actualmente sean re-trasplantes.[22] En los ojos con fracaso de injerto DMEK, los resultados del re-trasplante son favorables, recuperando la agudeza visual y recuperando la trasparencia corneal.[22] En nuestra gran revisión de la literatura de re-trasplante laminar endotelial, hemos verificado que la re-DMEK probablemente tiene resultados visuales comparables con las DMEK primarias y posiblemente tasas de rechazo similares, pero que es posible que la pérdida endotelial y el riesgo de LEGF sean superiores.[17] Postulamos que los resultados visuales de la re-DMEK dependen del *timing* de la cirugía, una vez que la re-intervención tardía puede asociarse a la

presencia de fenómenos fibroticos corneales anteriores que disminuyen el pronóstico visual.[17]

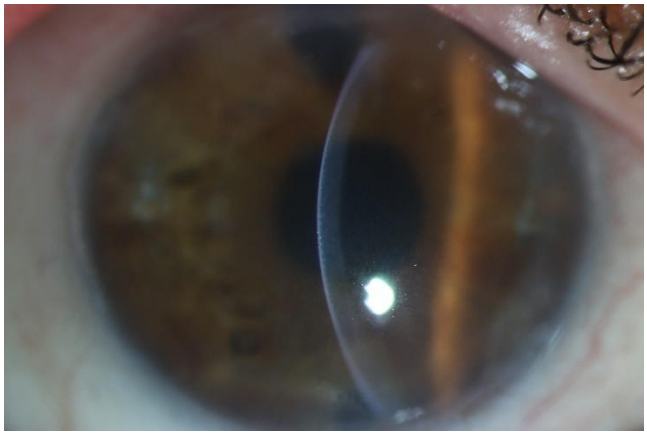
RECHAZO INMUNOLÓGICO DE INJERTO

El rechazo inmunológico tras DMEK es una complicación infrecuente, sin embargo, es una complicación potencialmente amenazadora para la supervivencia del trasplante y para la visión. El riesgo acumulativo de rechazo post-DMEK reportado es bajo, con las series más largas y con seguimientos de 5 a 10 años reportando un riesgo acumulativo de 2% a 9%.[5,19,21] De hecho, el perfil inmunológico del injerto DMEK es mucho más favorable que los de DSAEK y que los de queratoplastia penetrante.[16,23]

Los mecanismos inmunológicos de rechazo de injerto laminar posterior no son completamente conocidos. A pesar de que es probable que los mecanismos de inmunidad adaptativa mediados por células Th1 estén presentes (como en los ojos operados de QPP), se ha observado un aumento de interleucinas 5 y 8 en ojos con DMEK primarias fracasadas, que sugiere que hay mecanismos de inmunidad celular innata o mecanismos no-celulares de rechazo inmune en injertos DMEK. [24]

La presentación clínica del rechazo inmune de injerto DMEK puede ser distinta a la del rechazo endotelial de una queratoplastia penetrante. Muchas veces, los pacientes se presentan sin síntomas o poco sintomáticos, a pesar de que pueden presentarse también con franco edema corneal y disminución de agudeza visual (Figura 4). La presencia de la línea endotelial de Khoudadoust es infrecuente, y más frecuentemente se observan precipitados queráticos endoteliales aislados.

Figura 4: Rechazo inmunológico de injerto DMEK con descompensación corneal.



El manejo del rechazo inmunológico de DMEK se basa en su profilaxis y en su detección y tratamiento temprano y agresivo para prevenir sus complicaciones. La profilaxis se basa en la administración de corticoesteroides (CS) tópicos postoperatoriamente, inicialmente con dosis más elevadas y con disminución progresiva durante los primeros meses. El principal factor de riesgo para episodios de rechazo de DMEK parece ser la ausencia de profilaxis inmunosupresora; un estudio de 1000 ojos operados de DMEK observó 12 ojos con episodios de rechazo, de los cuales un 75% habían suspendido los corticoides tópicos, en algunos no por indicación clínica.[25] Los ojos con injertos corneales previos tienen mayor riesgo de rechazo inmunológico de injerto.[18] La duración de administración de CS tópicos post-DMEK no es consensual, pero se ha observado que la incidencia acumulativa de rechazo post-DMEK es significativamente más baja si la corticoterapía es mantenida durante los primeros 2 años postoperatorios. [26] Un meta-análisis reciente ha concluido que la utilización de un "*soft steroid"* (por ejemplo, la hidrocortisona 0.335% o la fluorometolona 0.1% de instilación diaria) pueden ser una alternativa a la prednisolona o a la dexametasona en la profilaxis del rechazo post-DMEK.[23] Nuestro grupo preconiza que la profilaxis del rechazo inmune post-DMEK sea con prednisolona acetato 0.1% o dexametasona 0.1% con frecuencia alta en las primeras semanas y con disminución progresiva durante los primeros 6-12 meses, con una dosis de mantenimiento con un durante un mínimo de 2 años (vigilando la presión intraocular y el nervio óptico); en algunos casos, principalmente los ojos con injertos corneales previos, preconizamos la CS tópica por período indefinido, ya que parecen ser ojos con un riesgo superior a las DMEK primarias (*Moura-Coelho et al., comunicación personal en el 8th World Cornea Congress, 2022*). El aspecto más

importante del tratamiento del rechazo es su detección precoz y tratamiento agresivo, reintroduciendo o aumentando la frecuencia de los CS tópicos. La presencia de episodios de rechazo de injerto DMEK resulta en pérdida endotelial aumentada, pero con el manejo correcto de un episodio de rechazo, el riesgo de fracaso parcial o completo de injerto DMEK es relativamente bajo, [21] sin embargo, no es despreciable, con un estudio de 12 ojos con rechazo de DMEK observando que un 16.7% de los ojos necesitaron re-transplante.[25]

ERROR REFRACTIVO RESIDUAL SIGNIFICATIVO

Las técnicas de queratoplastia laminar posterior tienen un perfil de predictibilidad refractiva superior a la queratoplastia penetrante, en particular la DMEK, la que algunos autores consideran un procedimiento refractivamente neutro. La DMEK se asocia a un cambio hipermetrópico, con un cambio promedio de equivalente esférico de +0.31 D y un cambio medio del astigmatismo variable entre el -0.60 y +1.11 D [16], y tiene habitualmente una estabilidad visual y refractiva elevada a partir de los 3-6 meses postoperatorios. Sin embargo, hasta el 35% de los ojos pueden tener un cambio refractivo superior a 1.00 D tras la DMEK, y hasta 32% de los ojos tienen cambios del astigmatismo por encima de 1.00 D; en ojos con cambios refractivos > 1.00 D tras DMEK, las “sorpresas refractivas” reportadas varían entre el 1.25-2.50 D de astigmatismo.[27] Estos cambios refractivos resultan de la deturgescencia corneal post-DMEK (que causa un cambio en la curvatura corneal posterior mayor que el cambio en la curvatura corneal anterior) y del astigmatismo inducido por la cirugía.

En ojos operados de catarata y DMEK (sea cirugía secuencial - catarata seguida de DMEK -, sea cirugía triple), se preconiza apuntar a un target refractivo residual entre -0.50 y -0.75 D de equivalente esférico residual, para compensar el cambio hipermetrópico. Sin embargo, el cambio hipermetrópico post-DMEK es de difícil predictibilidad, una vez que en algunos casos se observan aumentos inesperados de la curvatura corneal anterior. Esta “impredictibilidad relativa” refractiva post-DMEK ha sido uno de los frenos a la adopción de LIOs “Premium” en ojos con distrofia de Fuchs y operados de cirugía triple (catarata e implante de LIO combinada con DMEK).[28]

Algunos autores han valorado la posibilidad de corrección de errores refractivos residuales significativo post-DMEK a través de cirugía queratorefractiva con láser excimer.[27,29] Atendiendo a los cambios en la paquimetria y topografía corneal que ocurren tras la cirugía de DMEK, recomendamos posponer cualquier corrección con láser hasta que se confirme la estabilidad refractiva y topográfica y que la decisión de corrección de ametropía residual post-DMEK sea valorada de manera individualizada.

EDEMA MACULAR QUISTICO POST-DMEK

Respecto a las complicaciones de segmento posterior tras DMEK, la más frecuente es el EMQ; dicho esto, la aparición de EMQ post-DMEK es una complicación infrecuente, pero probablemente infra-reportada. La incidencia de EMQ post-DMEK (presencia de fluido intra- o sub-retiniano en la foveola) detectada por tomografía de coherencia óptica *spectral-domain* (SD-OCT) se encuentra entre el 0% y el 15.6%, pero la incidencia de EMQ con impacto visual (definido por la presencia de EMQ en SD-OCT en pacientes donde la agudeza visual postoperatoria es inferior a la esperada para el grado de trasparencia corneal y en la ausencia de hallazgos *de novo* en el polo posterior) está entre el 3.83% y el 9.36%.[30-32] Nuestro grupo ha observado una incidencia de 4.8% de EMQ post-DMEK con impacto visual, superior a la incidencia de EMQ pseudofáquico (EMQ-p) (*Moura-Coelho et al., aceptado para publicación; DOI: 10.1038/s41598-023-29127-5*). En la literatura, el tiempo promedio para aparición de EMQ post-DMEK varía entre las 5.2 semanas y los 4.3 meses [30,32,33], pero en la mayoría de los casos, el EMQ aparece durante el primer mes tras la DMEK, pudiendo ser detectado hasta los 6 meses.

La fisiopatología del EMQ post-DMEK es probablemente similar a la del EMQ-p, pero con la liberación aumentada de mediadores inflamatorios derivada de la manipulación del iris y el endotaponamiento con gas. En ojos operados de DMEK, ocurre un aumento de las citoquinas pro-inflamatorias IFN-γ, IL-8 y IL-10en comparación con ojos operados de catarata sin enfermedad corneal. [34]

El reconocimiento de factores de riesgo pre- y peri-operatorios es la primera estrategia para disminuir la incidencia de EMQ post-DMEK. Se han propuesto

algunos factores de riesgo como diabetes *mellitus*, historia de uveítis o historia previa de EMQ; membrana epiretiniana; lesión iridiana pre-DMEK; ojos operados de DMEK por otras indicaciones que no la distrofia del endotelio corneal de Fuchs (re-trasplantes corneales,[30,35] y otras causas secundarias de disfunción o fallo endotelial, como el edema bulloso iatrogénico o la disfunción endotelial relacionada con cirugía de glaucoma) [36-38]; y el GD con necesidad de *re-bubbling*. Es probable que en ojos "no-Fuchs" haya un microambiente pro-inflamatorio que predispone a la aparición de EMQ. Inoda et al. han observado que ojos operados de DMEK aislada tuvieron mayor incidencia de EMQ en comparación con los ojos operados de DMEK "secuencial", postulando que el tratamiento con anti-inflamatorios no esteroideos (AINEs) tras la cirugía de cristalino tendría efecto protector.[39] Sin embargo, otros autores han observado resultados distintos.[31,32,40] Se ha levantado la hipótesis de que el *re-bubbling* puede aumentar la liberación de prostaglandinas y otros mediadores inflamatorios por la manipulación repetida. [32,39,41] Sin embargo, la evidencia en la literatura de que la indicación para DMEK, de que el tipo de técnica quirúrgica y de que la necesidad de *re-bubbling* son factores de riesgo para EMQ post-DMEK es contradictoria.

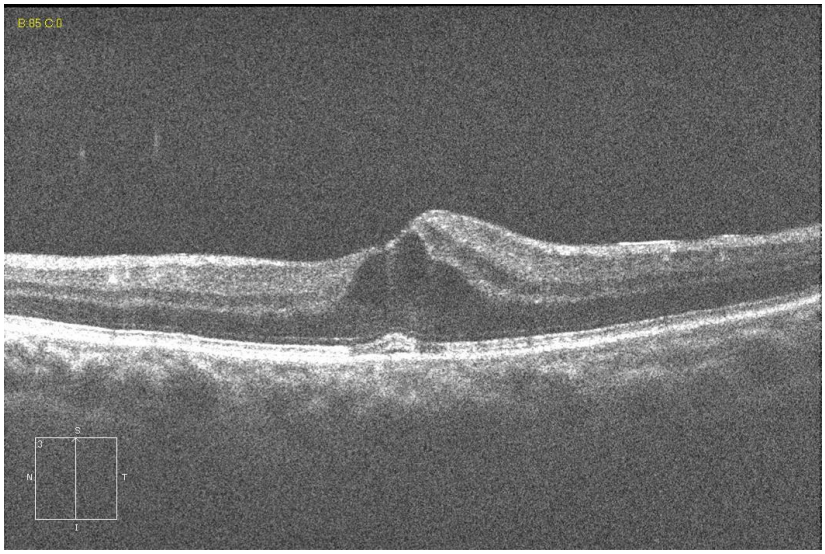
Hay algunos factores que podrán ser protectores de EMQ post-DMEK. Dapena et al. observaron una asociación entre la realización de iridotomía láser antes de la cirugía de DMEK y una menor incidencia de EMQ post-DMEK.[42] La utilización de AINEs en el período postoperatorio podría ser protector; pero la evidencia es extrapolada de los estudios que demuestran su efecto protector en el EMQ-p y también en el estudio de Kitazawa et al., donde se observó un efecto protector de los AINEs en la prevención de EMQ post-DSAEK.[37] Hoerster et al. observaron que un régimen de CS tópicos intensificado en el período postoperatorio precoz disminuye el riesgo de EMQ post-DMEK. En este estudio, los autores compararon dos grupos de pacientes operados de DMEK, uno tratado con CS tópicos 5 veces al día y el otro con CS tópicos cada hora en la primera semana postoperatoria (régimen intensificado) y observaron una incidencia de EMQ de 12% en el grupo que hizo CS 5 veces al día *versus* una incidencia de 0% en el grupo bajo régimen de CS intensificado.[33]

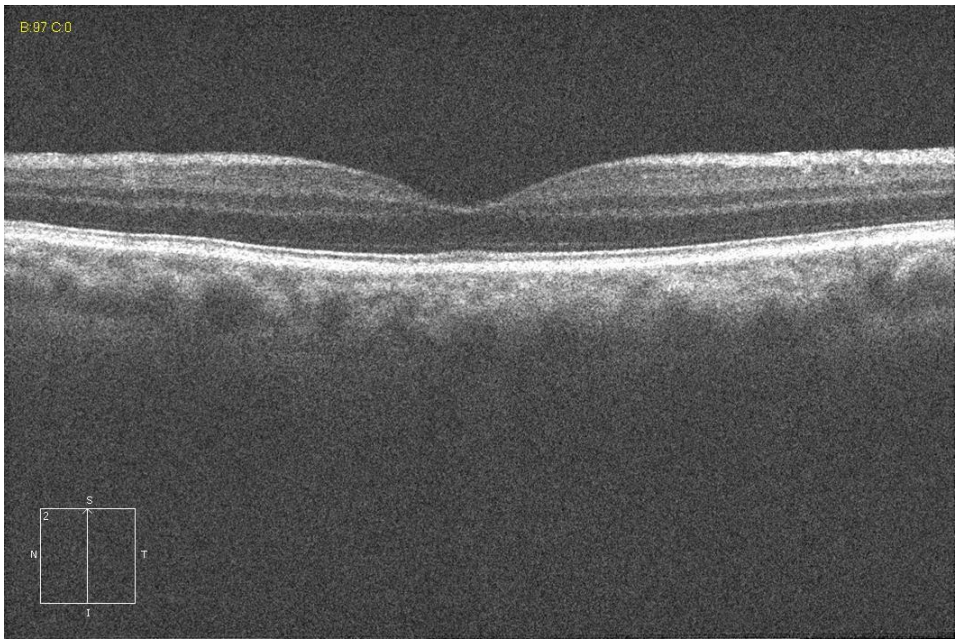
La primera estrategia del manejo del EMQ post-DMEK consiste en prevenir su aparición. En línea con los resultados de Hoerster et al., hemos adoptado la

estrategia de un régimen intensificado de CS tópicos en la primera semana post-DMEK como profilaxis del EMQ. Actualmente, no hay un protocolo estándar para el tratamiento del EMQ post-DMEK. Las terapéuticas de primera línea propuestas incluyen alguna combinación de aumento de la frecuencia de los CS tópicos, la adición de AINEs tópicos, la adición de acetazolamida oral e inyecciones subtenonianas de CS. Nuestra primera línea de tratamiento del EMQ post-DMEK consiste en añadir al régimen de CS tópico postoperatorio un AINE tópico y acetazolamida oral 250 mg cada 8 horas. Con nuestro régimen de primera línea, hemos observado una elevada tasa de éxito en la resolución del EMQ con impacto visual (*Moura-Coelho et al., aceptado para publicación; DOI: 10.1038/s41598-023-29127-5*), similar a los resultados de otros autores (Figura 5). En ojos refractarios a primeras líneas de tratamiento, se han utilizado CS intravitreos con éxito.

El EMQ post-DMEK tiene buen pronóstico, verificándose la resolución del edema macular y la mejoría de la agudeza visual después de iniciar la terapéutica en la gran mayoría de los casos (*Moura-Coelho et al., aceptado para publicación; DOI: 10.1038/s41598-023-29127-5)*. En la literatura se ha encontrado apenas un caso de EMQ post-DMEK, en el estudio de Hoerster et al. donde un paciente tuvo EMQ refractario a la inyección intravítrea de Ozurdex.[33]

Figura 5: Edema macular quístico (EMQ) post-DMEK documentado por tomografia de coherencia optica *spectral-domain* (Figura 5A). Tras tratamiento de primera línea con anti-inflamatorios no esteroideos y acetazolamida oral, se observó resolución del EMQ a las 4 semanas de seguimiento (Figura 5B).





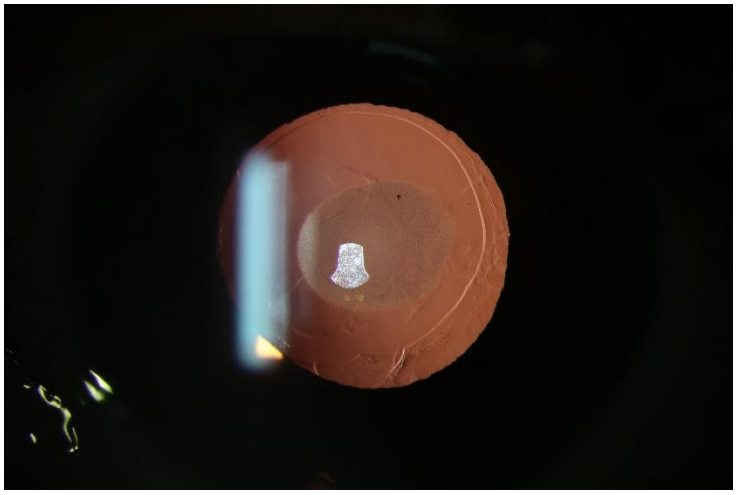
OPACIFICACIÓN DE LENTE INTRAOCULAR

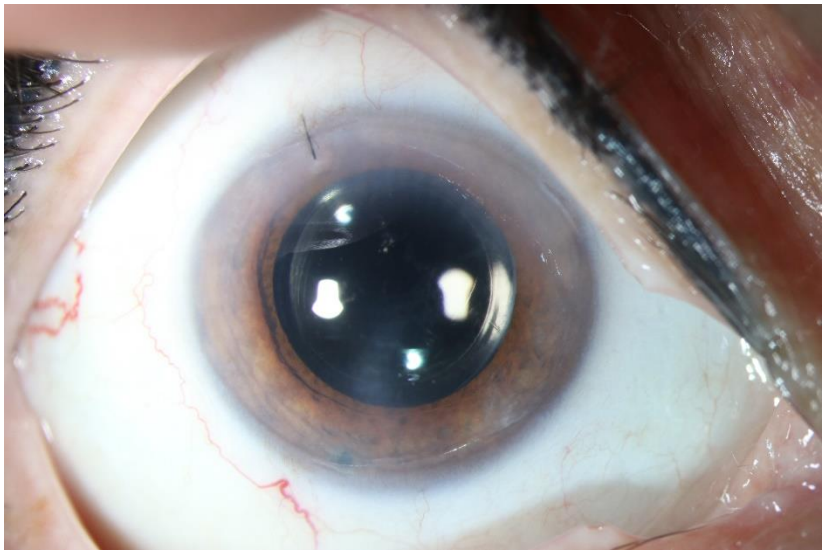
La opacificación de lente intraocular pseudofáquica (LIO) post-DMEK es una complicación infrecuente pero probablemente sub-reportada en la literatura, potencialmente amenazadora de visión y cuyo tratamiento puede poner en peligro la supervivencia del injerto de DMEK.[43] La opacificación de LIO tras DMEK es causada por el endotaponamiento con gas intraocular y resulta de la deposición de calcio y fosfato en la superficie anterior y sub-superficie de la LIO. La incidencia reportada de opacificación de LIO se encuentra entre el 0.44 y el 12.9% tras DMEK [44-46], siendo probablemente superior en ojos operados de DSEK o DSAEK. El material de la LIO puede ser el principal factor de riesgo para opacificación de LIO tras DMEK,

siendo mayor el riesgo con LIO hidrofílicas. [45-47]. Sin embargo, se han descrito casos de opacificación de LIO hidrófoba tras EK.[45,46] Otros factores de riesgo reportados incluyen la diabetes *mellitus*, la hipersensibilidad a los CS, y la necesidad de *re-bubbling* [45]; sin embargo, de nuevo es contradictorio si el *re-bubbling* es factor de riesgo para opacificación de LIO tras DMEK.[46]

El tiempo para la aparición de la opacificación de LIO varía entre pocas semanas hasta años después de la cirugía *(Moura-Coelho et al., comunicación oral en el EuCornea Congress, 2021)*. La opacificación de la LIO lleva a una disminución significativa de la calidad óptica ocular, lo que se traduce clínicamente en disminución de la sensibilidad al contraste y de la agudeza visual en los casos más severos. En casos con disminución de la agudeza visual (estimados en un 7-20% de los ojos con opacificación de la LIO), puede implicar la necesidad de explante de LIO (Figura 6), hecho que comporta riesgos de complicaciones oculares (por ejemplo, rotura de cápsula posterior y prolapso vítreo, EMQ postoperatorio, infección postoperatoria) y puede implicar una pérdida acelerada de células endoteliales del injerto donante de DMEK, pudiendo amenazar la supervivencia del injerto.[44,45] En nuestra experiencia, el recambio de LIO resultó en una recuperación visual rápida y significativa en ojos con opacificación severa de la LIO tras la DMEK *(Moura-Coelho et al., comunicación oral en el EuCornea Congress, 2021)*, en línea con los hallazgos de Lorenzana-Blanco et al.[46]

Figura 6: Opacificación de lente intraocular (LIO) hidrofílica con impacto clínico a los dos años tras la cirugía DMEK (6A), con disminución de la agudeza visual (AV) de 20/30 para 20/50 Snellen. Tras la cirugía de recambio de LIO, la córnea mantuvo su trasparencia y se observó recuperación rápida de la AV para 20/25 Snellen (6B).





COMPLICACIONES ESPECÍFICAS DE DMEK FÁQUICA

El interés en realizarse DMEK preservándose el cristalino ("DMEK fáquica") ha aumentado en los últimos años, por la posibilidad de preservar el cristalino sin catarata en pacientes jóvenes con patología del endotelio corneal y por la posibilidad de realizarse la cirugía de cristalino e implante de LIO posteriormente a la deturgescencia corneal inducida por la DMEK, lo que permite mejorar la precisión refractiva del procedimiento. Sin embargo, entre 13% y 40% de estos ojos necesitarán de cirugía de cristalino en el corto-medio plazo [48,49]; un meta-análisis reciente observó una tasa promedia de cataratógenesis en ojos operados de DMEK fáquica de 9.5%, pero altamente variable, variando entre 0.4% y un 72%.[50] En estos

ojos, la cirugía de cristalino implica una pérdida endotelial que puede variar entre un 4% y un 25% (promedio reportado de un 11% de pérdida endotelial a los 6 meses), lo que comporta un riesgo para la supervivencia a largo plazo del injerto DMEK.

OTRAS COMPLICACIONES POSTOPERATORIAS TRAS CIRUGÍA DE DMEK

Otras complicaciones raras tras la cirugía de DMEK, pero con consecuencias catastróficas para la visión, incluyen la queratitis infecciosa y la endoftalmitis, el desprendimiento retiniano, el desprendimiento de coroides (DC) y la hemorragia expulsiva.

La incidencia de DC tras DMEK no es conocida, pero se estima en un 0.05% [51]; un gran estudio de más de 94 mil ojos operados de queratoplastia endotelial en los Estados Unidos (no distinguiendo entre DSAEK y DMEK) observó una incidencia acumulativa de 0.05% a los 90 días.[52] La mayor parte de los DC son hemorrágicos, sin embargo, también pueden ser serosos. Es posible que el DC post-DMEK tenga factores de riesgo comunes a otras cirugías intra-oculares, como edad avanzada del paciente, hipertensión arterial sistémica, miopía magna, cirugía filtrante de glaucoma, afaquia, y uso de anticoagulantes orales. El manejo del DC postoperatorio es igual a lo del DC postoperatorio en otros casos. La hemorragia expulsiva, posiblemente la complicación más temida por todos los cirujanos intraoculares, es una complicación rarísima tras DMEK, apenas con un caso reportado de hemorragia pre-expulsiva en un paciente con edad muy avanzada, glaucoma avanzado, penfigoides ocular cicatricial e injerto de DSAEK previo fracasado.[53]

El estudio de Zafar et al. de casi 95 mil ojos operados de queratoplastia endothelial observó una incidencia acumulativa de 0.03% de endoftalmitis infecciosa a los 90 dias de seguimiento postoperatorio.[52] Sin embargo, su estudio no diferenció entre DSAEK y DMEK,[52] y en la literatura sólo hay 2 reportes de caso. [54,55] A pesar de la incidencia muy baja de endoftalmitis post-DMEK,, la utilización de cefuroxima intra-cameral al final del procedimiento es prudente, ya que es una estrategia ya ampliamente adoptada en cirugía de cataratas (con demostrada efectividad en

disminuir la incidencia de endoftalmitis en el importante estudio de endoftalmitis de la *European Society of Cataract and Refractive Surgeons*) [56] e ya que ha demostrado ser segura para el injerto DMEK, sin pérdida endotelial acelerada ni aumento de riesgo de *re-bubbling.* [57] La endoftalmitis secundaria a la contaminación de injertos donantes tras queratoplastia laminar posterior es todavía más rara, con 9 casos reportados en la literatura.[58]

CONCLUSIONES

Las complicaciones tras la cirugía de DMEK pueden ocurrir en cualquier momento del seguimiento postoperatorio y tener implicaciones para la supervivencia del injerto y para la visión. En el período postoperatorio precoz (primeros 3 meses), las principales preocupaciones son el GD con necesidad de *re-bubbling,* que es la complicación más frecuente en este período, estando indicado el *re-bubbling* precoz en los casos de GD de mayores dimensiones y más próximos al centro de la córnea causando edema corneal con significado clínico; y el PGF.

Tras los primeros meses post-DMEK y una vez asegurado el funcionamiento inicial del injerto DMEK, la supervivencia del injerto es influenciada principalmente por la pérdida de células endoteliales, y también por la aparición y manejo de algunas complicaciones. La tasa de rechazo inmunológico de injerto DMEK es muy baja y su pronóstico habitualmente favorable, sin embargo, no es una complicación menospreciable, siendo su profilaxis fundamental para asegurar la supervivencia a largo plazo del injerto. La pérdida de células endoteliales tras la DMEK es más importante en los primeros meses postoperatorios, pero estabiliza, verificándose un perfil de pérdida endotelial a largo plazo lineal y favorable en comparación con la pérdida endotelial a largo plazo de injertos de queratoplastia penetrante. A medio-largo plazo, la pérdida endotelial es el principal factor que influencia la supervivencia de la DMEK, y su prevención (a través de una cuidadosa técnica quirúrgica, del control postoperatorio de la PIO y del manejo adecuado de algunas complicaciones postoperatorias) es fundamental para disminuir el riesgo de fracaso tardío de injerto y retrasar la necesidad de re-trasplante corneal.

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CHAPTER 19

Cataract Surgery in Combination with Corneal Surgery

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Introduction

Cataract extraction (CE) is currently one of the most commonly performed surgeries worldwide, since it is a quick procedure that can be performed under topical or local anaesthesia, and since it leads to rapid visual recovery in most cases with significant improvement in vision and increased spectacle independence. With the increasing number of CE performed, surgeons are encountering more often patients with concurrent corneal diseases, including keratoconus (KC), corneal opacities / scars or corneal degenerations, and different congenital abnormalities or corneal dystrophies, with Fuchs' endothelial corneal dystrophy (FECD) being the most common. Conversely, central corneal transplant procedures and cataract surgery are one of the most frequent combinations that the corneal surgeons have to deal with. Another important aspect is the association between corneal disease and the earlier onset of cataract, as occurs in KC, in infectious keratitis and herpetic eye disease (HED), and in eyes with corneal grafts. Importantly, cataract surgery has the potential to contribute to the progression of pre-existing corneal disease, and similarly,

corneal disease can limit surgical techniques of CE and may be the cause of poor outcomes after CE.

Decision-making process – preoperative assessment

Patient evaluation

In eyes with concurrent corneal pathology and cataract, surgeons need to consider whether to perform simultaneous corneal surgery and CE (single-stage surgery) or to perform sequential surgery, and in such cases to decide which surgery to be performed first. The decision to perform single-stage surgery versus sequential surgery depends on a number of factors, including the stage of corneal disease, the monocular or binocular status of the patient, and the relative contribution of corneal and lens diseases to the visual impairment.

The status of the cornea should be assessed using multiple approaches. The clinical history should be directed towards signs and symptoms suggestive of corneal dysfunction. For instance, visual symptoms that are worse in the morning upon awakening suggest corneal endothelial failure as the main cause of patient's visual impairment. In these cases, the surgeon may recommend the patient to visit the clinic in the early morning to assess visual acuity and the presence of corneal oedema in the slit-lamp or by pachymetry. The relative contribution of the corneal opacity or irregularity to the visual impairment should be determined by a diagnostic rigid gas-permeable contact lens (RGPCL) refraction compared with the best-corrected spectacle visual acuity (BCVA), with a difference of more than 2-lines of Snellen visual acuity being suggestive of the blur being due to clinically significant corneal irregular astigmatism; this may be complemented by determination of the degree of irregular astigmatism by corneal topography. Morphologic examination should include a general evaluation of the ocular adnexa, including eyelid and eyelash position, evaluating the presence of eyelid diseases with impact in the ocular surface or risk of delayed wound healing after surgery (e.g., atopic dermatitis, rosacea, anterior and posterior blepharitis), conjunctival health, and assessment of tear film function and quality. Corneal examination under the slit-lamp biomicroscope is important to characterize the location, size and density of a corneal opacity and its relation to the visual axis to determine the relative contribution of the opacity to visual impairment; determination of corneal thickness and search for signs of corneal endothelial failure (corneal guttae, Descemet's membrane thickening, stromal oedema, presence of epithelial microcysts or bullae); and to assess factors associated with wound healing after intraocular surgery (e.g., signs of limbal stem cell deficiency (LSCD) and signs of neurotrophic keratopathy (NK)).

Determining the relative contribution of the cataract to the visual impairment involves characterization of symptoms and signs. Patients with cataract may complain more of difficulty with nighttime driving and increased glare, and may have monocular diplopia or polyopia. Slit lamp biomicroscope characterization of the lens size, position and mobility, and the subtype and density of cataract are important to determine whether the severity of the cataract correlates to the level of visual impairment and patient symptoms. Comparison of the cataract density with that of the fellow eye provides additional information, for instance in cases where there is significant asymmetry in visual acuity to determine whether the cataract is the main cause of blur. Assessment of the ocular fundus (under pharmacological mydriasis whenever possible) is essential to determine whether there is retino-neural integrity which may compromise postoperative results after corneal and/or cataract surgery.

Adjunctive preoperative testing

Additional tests are required in the preoperative evaluation of the corneal or crystalline lens components of visual impairment. Corneal topography/tomography provides detailed analysis of the corneal curvature and irregularity (keratometry maps and aberrometry), corneal thickness (pachymetry maps), anterior and posterior corneal curvature and elevation maps. Corneal densitometry (CD) is an add-on Scheimpflug technology which may offer more information on the corneal backscattering and its relative contribution to visual impairment.[1] In addition, novel Scheimpflug-based topographers allow characterization of lens opacities and density. Anterior segment optical coherence tomography (AS-OCT) provides information on size, density and depth of corneal opacities and irregularities, allows visualization of the crystalline lens and anterior chamber, and may be a helpful adjunctive to slit-lamp examination. Specular microscopy or confocal microscopy provide structural evidence of corneal endothelial dysfunction, including decreased endothelial cell density (ECD), changes in the endothelial mosaic, corneal endothelial cell pleomorphism and polymegathism, and presence of guttae. However, corneal pachymetry is the only readily available objective measurement of the endothelial pump function, and pachymetry readings (especially their comparison over time) may help in determining the risk of corneal decompensation. In cases of suspected NK (e.g., patients with HED or patients with previous corneal grafts), corneal esthesiometry must be performed, as impaired corneal sensation may affect corneal healing after intraocular surgery and will have implications in cases where keratoplasty is performed. To date, the HD Analyzer (Visiometrics SL, Terrassa, Spain) is the only readily available system that objectively

measures visual quality and scatter in the eye, and the objective scattering index (OSI) is a sensitive and efficient tool to detect and correlate cataract severity and visual quality.[2]

Adjunctive preoperative testing to determine the status of the retina and optic nerve should include a posterior segment OCT. Routinely performing macular OCT in routine cataract surgery candidates has been shown to improve detection of macular pathology in up to 25% of eyes,[3] and in eyes with corneal oedema or opacities undergoing CE this proportion may even be higher (provided that good quality OCT scans can be acquired, which may not be the case in eyes with severe corneal oedema, significant corneal opacities, or very dense cataracts). In eyes with severe corneal disease or very dense cataract precluding visualization of the ocular fundus, ocular ultrasonography should be performed to assess the vitreous, the retina and the optic nerve. Laser interferometry with a Rodenstock retinometer, the potential acuity meter test, and electrophysiologic testing may be helpful to determine retino-neural function in these cases. Finally, artificial intelligence technologies, including deep-learning algorithms, that analyse corneal and lens imaging data and characterize the cornea pathology and the crystalline lens density are likely to improve the understanding of the relative contribution of each disease to the visual impairment and to improve decision-making in these complex cases.[4-7]

Surgical technique in combined cataract and corneal surgery

Combined penetrating keratoplasty and cataract extraction

In cases requiring penetrating keratoplasty procedure (PKP) and CE, the options include performing a combined surgery of PKP plus CE (with or without intraocular lens (IOL) implantation) or performing PKP first, and CE + IOL implantation at a later stage (sequential surgery). Although performing CE sequential surgery has some advantages – particularly safety and improved refractive predictability, there are several drawbacks to this approach, including the need for multiple procedures, slow visual rehabilitation, and endothelial damage during cataract surgery. In addition, there are no significant benefits in final visual results between triple surgery (PKP + CE + IOL implantation) and non-simultaneous procedures over the long term.[8] Eyes with hard cataracts with previous PKP grafts may benefit from extracapsular cataract extraction (ECCE) rather than phacoemulsification, due to significantly lower rates of endothelial cell loss.[9]

In those cases of combined PKP + CE surgery, the decision to perform phacoemulsification versus ECCE will depend on a number of factors, including the severity of corneal opacity/oedema limiting visualization and the cataract density. Phacoemulsification with IOL implantation may be performed before corneal trephination if the corneal opacity is not dense enough to preclude acceptable visualization during surgery (Figure 1). Strategies to facilitate phacoemulsification in this setting include the following: selecting the best position to provide maximum clear working field; use of a surgical microscope with good optics and the best possible light intensity; the use of dispersive Ophthalmic Viscosurgical Devices (OVD) over the corneal epithelium; the use of trypan blue 0.01% dye for anterior capsule staining; and endoilluminators. Intracameral endoillumination provides a 3D image but is held with the surgeon's nondominant hand and, and may increase the risk of Descemet membrane injury with repeated movements; Chandelier retroillumination allows surgeons to use both hands during phacoemulsification, but requires a pars plana incision and vitreoretinal instrumentation. More recently, slit illumination of the surgical microscope has been proposed for patients with coexisting corneal opacities, enhancing the red reflex, contrast, and depth perception.[10] The incision placement should depend on the location of the opacity, again ensuring maximum clear working field. The anterior circular continuous capsulorhexis should be created with the aid of trypan blue to improve visibility, and retroillumination improves visualization of the rhexis against the red reflex. Nucleofractis and irrigation/aspiration can be performed as standard cataract surgery, but some modifications can be adopted to improve visualization, including performing emulsification of each fragment "in situ" to increase the amount of red glow for further chopping, performing emulsification only in visible pupillary area, preferring bimanual irrigation/aspiration; some surgeons advocate trypan blue staining of the posterior capsule.[11]

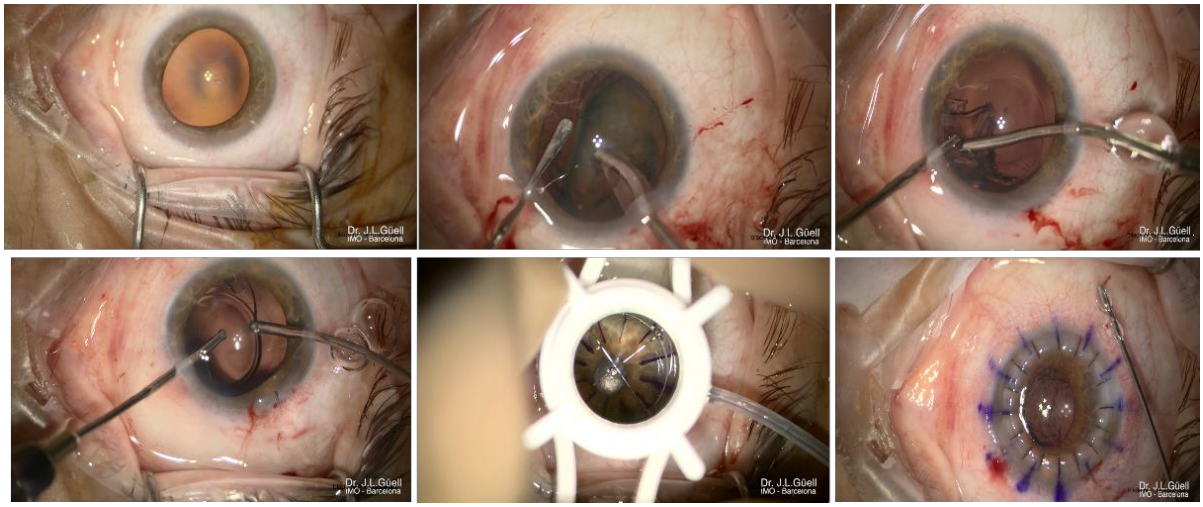


Figure 1. Combined penetrating keratoplasty and cataract extraction. Because the corneal opacity did not preclude adequate surgical visualization, phacoemulsification and intraocular lens implantation was performed before corneal trephination and corneal grafting.

In eyes with dense or diffuse corneal opacity, the main issue in performing combined surgery is that CE is performed "open-sky", with the attending risks of vitreous loss and expulsive haemorrhage due to altered anterior chamber and lens-iris diaphragm dynamics and abnormal light reflexes in the "open-sky" situation (Figure 2). The effort in this setting must be focused towards a safe cataract surgery and in-the-bag IOL implantation. Obtaining a soft eye is critical for success, for instance using a Honan balloon before starting the procedure; preoperative intravenous mannitol 20% may also be considered. We usually start by fixating a Flieringa ring to the sclera before performing corneal trephination. After excising the patient's corneal button, anterior capsulorrhexis is performed (ideally a continuous curvilinear capsulorhexis); to counteract the positive posterior pressure that occurs naturally in open-sky surgery, the surgeon may apply posterior pressure on the centre of the nucleus while the capsulorhexis is being performed, to reduce the risk of rhexis extension toward the equator. Some authors have proposed performed core vitrectomy before performing a triple PKP procedure in patients at high risk for increased posterior pressure.[12] Another possible strategy is the use of a temporary keratoprosthesis (TKP anterior segment model with 1.5 mm depth, Eckardt® temporary keratoprosthesis, DORC) (Figure 3). The nucleus can be manually expressed after thorough hydrodissection using bimanual push and pull hooks, followed by manual cortex aspiration using a Simcoe or a McIntyre irrigation/aspiration cannula; all cortex must be cleaned to minimize postoperative inflammation which will be injurious to the corneal graft. The IOL can then be implanted at the same surgical time in the posterior

chamber (triple surgery PKP + CE + IOL), or at a later stage in the ciliary sulcus (secondary IOL implantation - 2-stage procedure). We consider that a 2-stage procedure of PKP + CE followed by secondary IOL implantation combines the benefits of triple surgery (faster visual rehabilitation and reduced endothelial cell damage to the graft) and of sequential PKP followed by CE + IOL implantation (refractive predictability). Addressing IOL power determination with stable refraction and stabilized keratometric readings after graft suture removal improves the refractive accuracy, and allows for the use of toric IOLs to reduce post-keratoplasty astigmatism (Figure 4).[13]

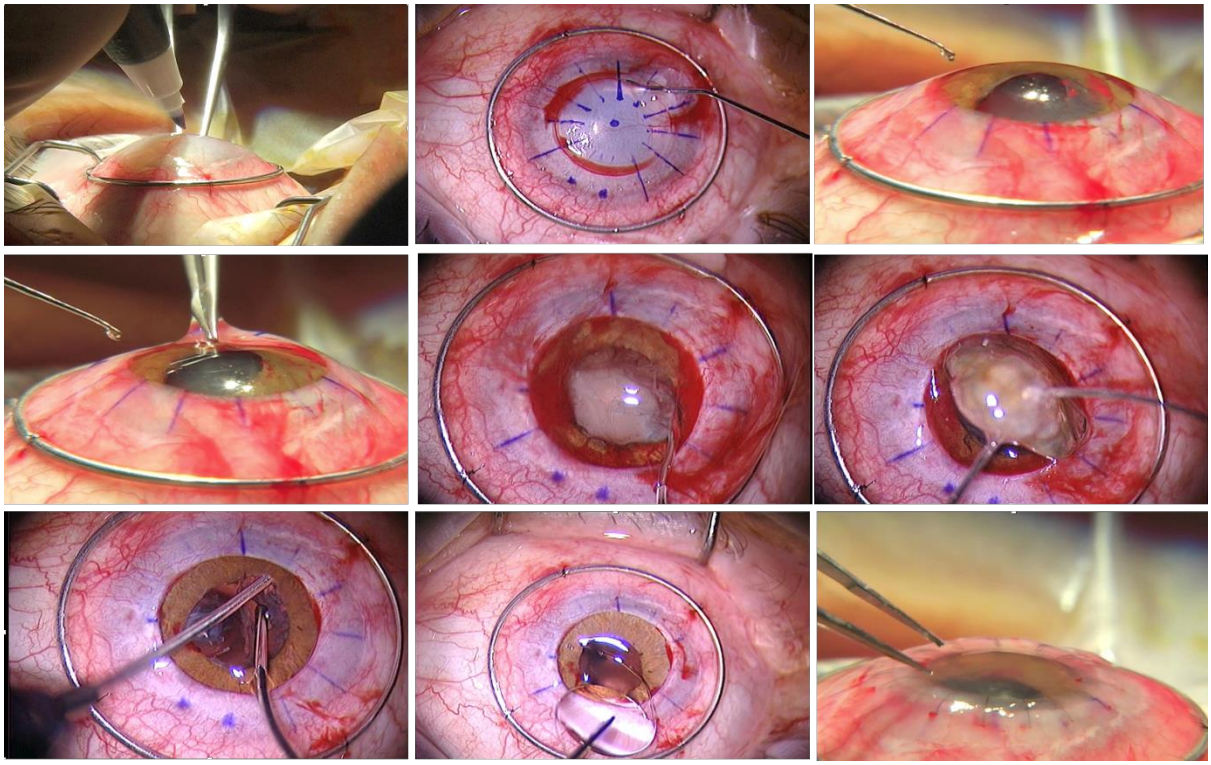


Figure 2. Combined penetrating keratoplasty with open-sky cataract extraction. Due to severe corneal opacity, corneal trephination was performed, followed by extracapsular cataract extraction (notice that a Flieringa ring is used before trephination). In this case, an intraocular lens was implanted before the corneal graft was sutured, although we currently consider that secondary IOL implantation may yield more predictable refractive results.

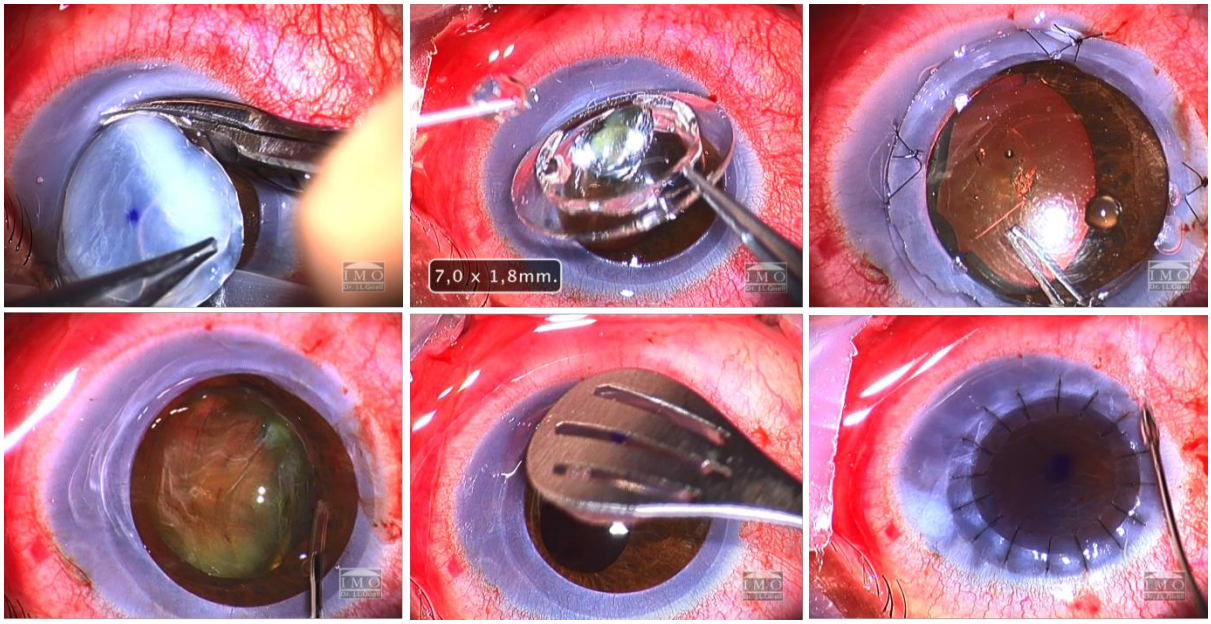


Figure 3. Combined penetrating keratoplasty with cataract extraction. In this case with a dense cataract, a temporary keratoprosthesis was used to perform capsulorhexis; the cataract was then safely extracted in "open-sky" and a full-thickness graft sutured.

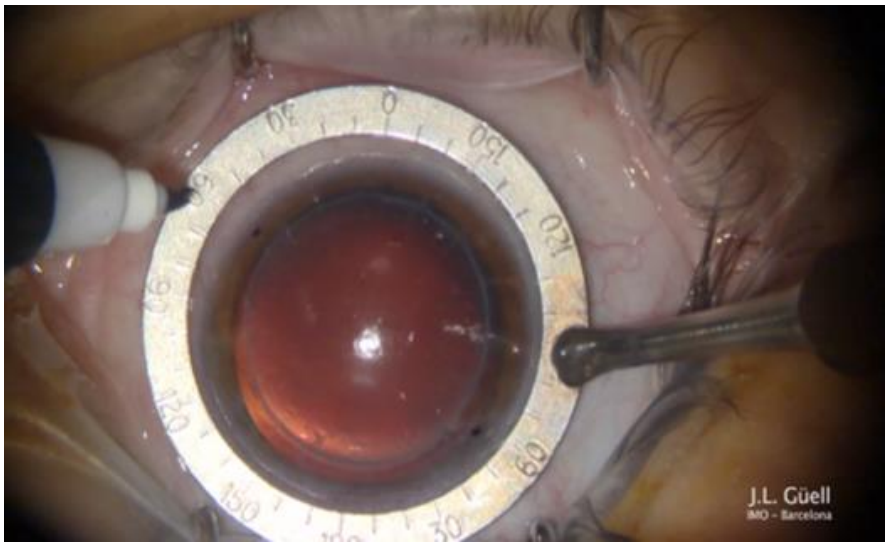


Figure 4. Marking the axis for toric IOL implantation after cataract extraction in a post-PKP eye.

In any case (combined or sequential surgery), unacceptable postoperative residual refractive errors may occur at PKP, and refractive enhancements may be required. These may include relaxing incisions, arcuate keratotomy incisions (AK) with or without compression sutures (Figure 5), corneal wedge resection, Excimer Light Amplification by Stimulated Emission of Radiation (Laser) keratorefractive surgery (photorefractive keratectomy (PRK) or Laser in situ keratomileusis (LASIK)), intrastromal corneal ring segments (ICRS), or

piggyback IOLs. Manual or Femtosecond Laser-assisted AKs have shown to be safe and effective in reducing refractive cylinder and improving unaided and spectacle-corrected visual acuity, however reduction of astigmatism is highly variable (changes in astigmatism may range between 30-90%), AKs do not correct the sphere refractive error, tend to induce myopic refractive shift, and may have unpredictable results.[14]

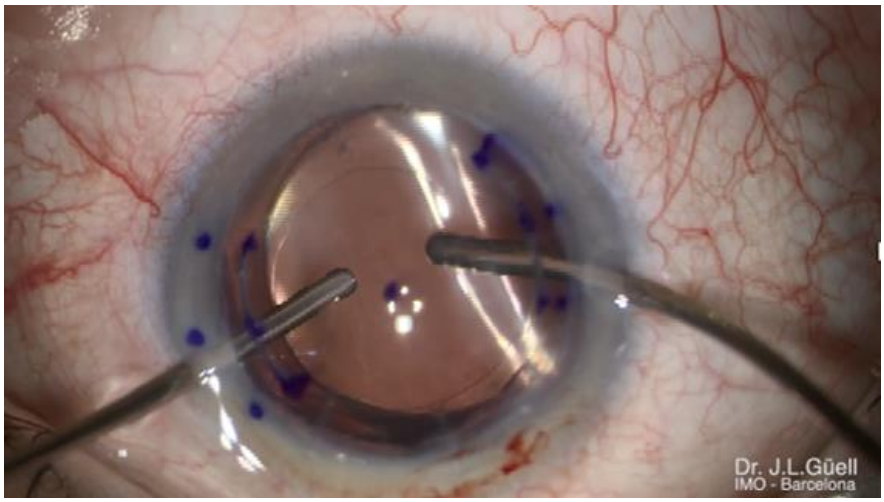


Figure 5. Combined arcuate keratotomy incisions and cataract extraction with IOL implantation in a post-PKP eye.

In eyes with complex anterior and posterior segment disease (e.g., penetrating trauma with large oedematous corneal wounds or corneal blood staining, cataract and retinal detachment), the use of a TKP (Eckardt® temporary keratoprosthesis posterior segment model with 2.8-mm cylinder depth, DORC) allows for a clear surgical view of the cataractous lens and posterior segment, avoiding the need to perform open-sky CE and vitrectomy or corneal transplantation followed by vitreoretinal surgery. Total thickness is trephination is performed, the TKP is placed and sutured, then the vitreoretinal procedure is performed, and after retinal surgery is concluded, the TKP is removed and a PKP graft can be sutured. This technique allows globe preservation in a high proportion of cases, with good rates of retinal reattachment with low rates of graft rejection and reduced risk of graft failure compared with keratoplasty followed by vitreoretinal surgery.[15,16]

Combined anterior lamellar keratoplasty and cataract extraction

The same principles can be applied in cases of anterior lamellar keratoplasty (ALK) and cataract ("ALK triple"),[17] with the (fundamental!) difference that CE is performed in a

"closed" eye rather than as an open-sky surgery. If the corneal opacity is not dense enough to preclude acceptable visualization during surgery, phacoemulsification and IOL implantation can be performed before corneal partial trephination.[18] Otherwise, corneal trephination is performed as in a standard lamellar surgery. Deep anterior lamellar keratoplasty (DALK)-triple procedure can be safely performed with phacoemulsification through bare predescemetic layer (Dua's layer) owing to its strength and clarity in cases where a type-1 big-bubble is achieved, but in eyes where a type-2 big bubble is obtained, attempting phacoemulsification can lead to sudden rupturing of the Descemet's membrane and compromise the corneal allograft outcomes.[19] Strategies to minimize damage to the host's endothelial cell layer include use of dispersive viscoelastic and low parameters (low vacuum and flow rates); the phaco-rolling technique also requires less energy to emulsify the nucleus.[20]

The same considerations regarding post-PKP refractive enhancements apply in the setting of post-DALK refractive enhancements,[21] including relaxing incisions and AK,[22] PRK,[23] and femtosecond laser-assisted LASIK,[24,25] small incision lenticule extraction,[26,27] ICRS, and piggyback pseudophakic IOLs. Likewise, secondary IOL implantation is possible and may improve refractive results (Figure 6).

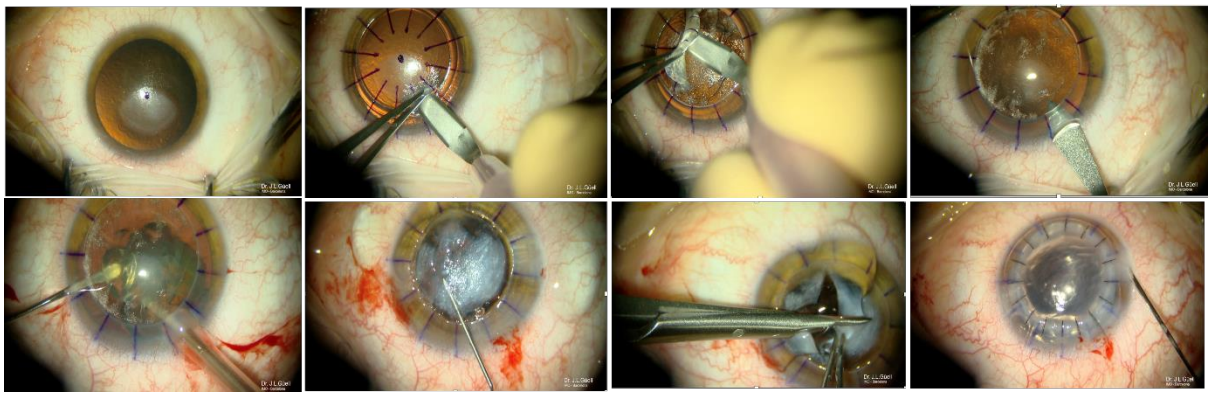


Figure 6. Combined anterior lamellar keratoplasty and cataract extraction. In this case, anterior stromal opacity allowed for phacoemulsification to be performed before attempting the visco-bubble technique for DALK. The decision was to perform secondary IOL implantation, to improve refractive outcomes.

Combined posterior lamellar keratoplasty and cataract extraction

Fuchs' endothelial corneal dystrophy is a bilateral, non-inflammatory, progressive endothelial cell loss leading to corneal oedema and visual dysfunction. Key features in FECD include presence of corneal guttae, folds in Descemet's membrane, stromal oedema, and microcystic epithelial edema. It was historically a frequent indication for keratoplasty, and is currently the most common indication for endothelial keratoplasty (EK).[28] The coexistence of FECD and cataract is not uncommon, and the surgeon will need to decide whether to perform CE alone or to combine CE and keratoplasty. The main advantage in performing CE first is that the need for keratoplasty may be avoided or significantly delayed in many cases of FECD. One study has reported that up to 25% of patients may regain significantly better vision after CE surgery to the point that EK was deferred.[29] However, keratoplasty plus CE will be indicated in cases where signs and symptoms are suggestive of endothelial cell dysfunction and a higher risk of corneal decompensation following CE: impaired subjective morning visual acuity with improvement of symptoms during the day; pachymetry >640 μm; endothelial cell density < 500 cells/mm^2. Having the patient coming to the clinic in the early hours to assess morning myopic shift and increased glare paralleling increased corneal thickness may be helpful in confirming corneal endothelial dysfunction.[30] Novel questionnaires may be included as part of a comprehensive evaluation of FECD, including the V-FUCHS (Visual Function and Corneal Health Status) instrument which allows for standardized quantification of visual disability in FECD and may aid in determining which individuals may benefit from intervention.[31] Certain corneal tomography parameters may help predicting FECD patients at risk of corneal decompensation after uncomplicated CE; one study found that loss of regular isopachs in pachymetry maps and displacement of the thinnest point of the cornea were independent and clinically important risk factors for progression and intervention.[32]

The same rationale can be applied in the setting of phakic IOL-induced accelerated endothelial cell loss or corneal decompensation (Figure 7). We have found that DMEK (Descemet membrane endothelial keratoplasty) is surgically feasible in eyes with phakic intraocular lens (pIOL)-associated corneal decompensation, resulting in early, clinically significant visual improvement, and with a high proportion of eyes reaching high levels of BCVA and very good refractive outcomes (*Moura-Coelho N., Güell JL., paper under review*). We have observed DMEK to reach better visual and refractive results in these eyes in comparison with published studies of DSAEK for this indication.[33] However, these eyes

may have an increased rate of endothelial cells loss following DMEK and an increased risk of late endothelial graft failure (LEGF). Although some authors have advocated simultaneous pIOL explantation and endothelial keratoplasty (EK),[34] we consider that a staged approach is preferable in this setting because of the risk of intraoperative bleeding during explantation which would complicate DMEK surgery, and because we believe that if the pIOL explantation (with/without refractive lens extraction (RLE)) procedure is uneventful, some patients may retain sufficiently acceptable BCVA to delay or prevent DMEK surgery.

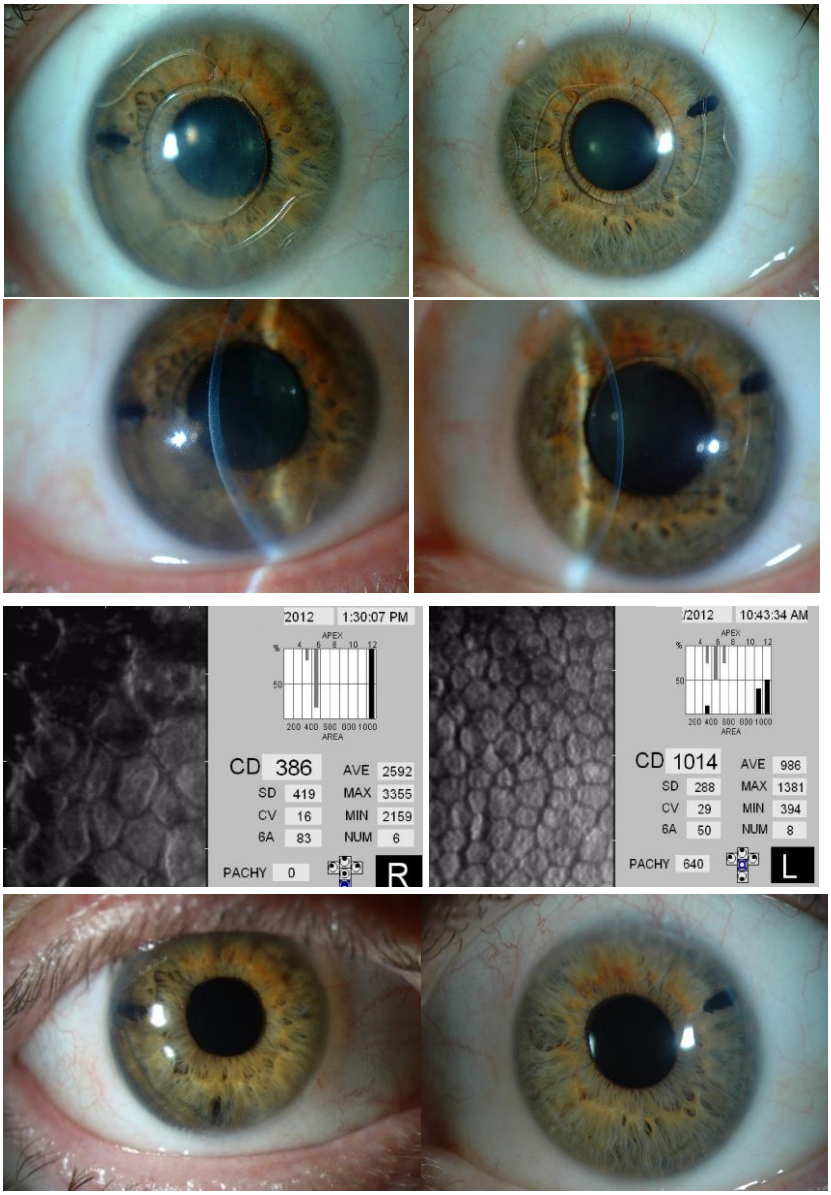


Figure 7. Anterior segment photographs (upper images)) of a patient with accelerated endothelial cell loss due to angle-supported phakic IOL implanted 12 years earlier, as evidenced by specular microscopy (middle)). The right eye (BCVA = 20/30) had signs of corneal endothelial failure, and so the decision was to perform a 2-stage surgery, with phakic IOL explantation plus phacoemulsification and in-the-bag IOL implantation followed by DMEK 10 weeks later, achieving a final BCVA of 20/20 $^{-1}$ and a clear cornea (lower images). One year later, despite a low endothelial cell count and a pachymetry of 640 µm, the left eye (BCVA 20/60 $^{+1}$) underwent uncomplicated phakic IOL explantation, phacoemulsification and in-the-bag IOL implantation and achieved good visual acuity (BCVA = 20/25) without corneal decompensation (lower image), eventually requiring a DMEK graft more than 7 years after cataract surgery.

Endothelial keratoplasty poses a challenge for IOL selection cataract surgery. In eyes undergoing CE and at risk for endothelial cell damage and/or corneal decompensation, and in eyes undergoing sequential CE then EK or triple EK surgery, hydrophobic IOLs should be preferred over hydrophilic or "hybrid" IOLs, since IOLs with a higher water content have a higher risk of IOL opacification after EK surgery due to calcium phosphate deposits on the surface or in the substance of the IOL. IOL opacification after EK may occur in 0.44-10% of all EK cases, and proposed risk factors include the hydrophilic IOL material and the need for re-bubbling and/or repeat EK grafting, since they imply repeated contact of air or gas with the surface of the IOL. IOL opacification after EK is associated with worse visual acuities, and if significant opacification occurs, the only possibility is to perform a IOL explant/exchange, which may lead to increased graft endothelial cell loss *(Moura-Coelho N., Güell JL., personal communication)* and pose a risk to graft survival.[35-37] Earlier studies found that refractive surprises > 1.00 D may occur in up to 35% of eyes after DMEK, and although DMEK tends to induce small changes in astigmatism, up to one third of eyes may experience a change in cylinder > 1.00 D. The degree of hyperopic shift is larger after DSEK/DSAEK (Descemet-stripping (automated) endothelial keratoplasty).[38] To account for the hyperopic shift that occurs after DMEK, the target refraction should range between -0.50 and -1.25 D. The Haigis IOL formula may have the highest refractive accuracy compared with other formulas (even newer formulas), and is currently the formula of choice of the authors.[39-41]

The main issue with refractive accuracy in FECD (plus cataract) eyes is an overestimation of corneal power, largely due to posterior corneal changes that disrupt the corneal anterior-posterior relationship and lead to misestimation of post-DMEK corneal power (Figure 8).

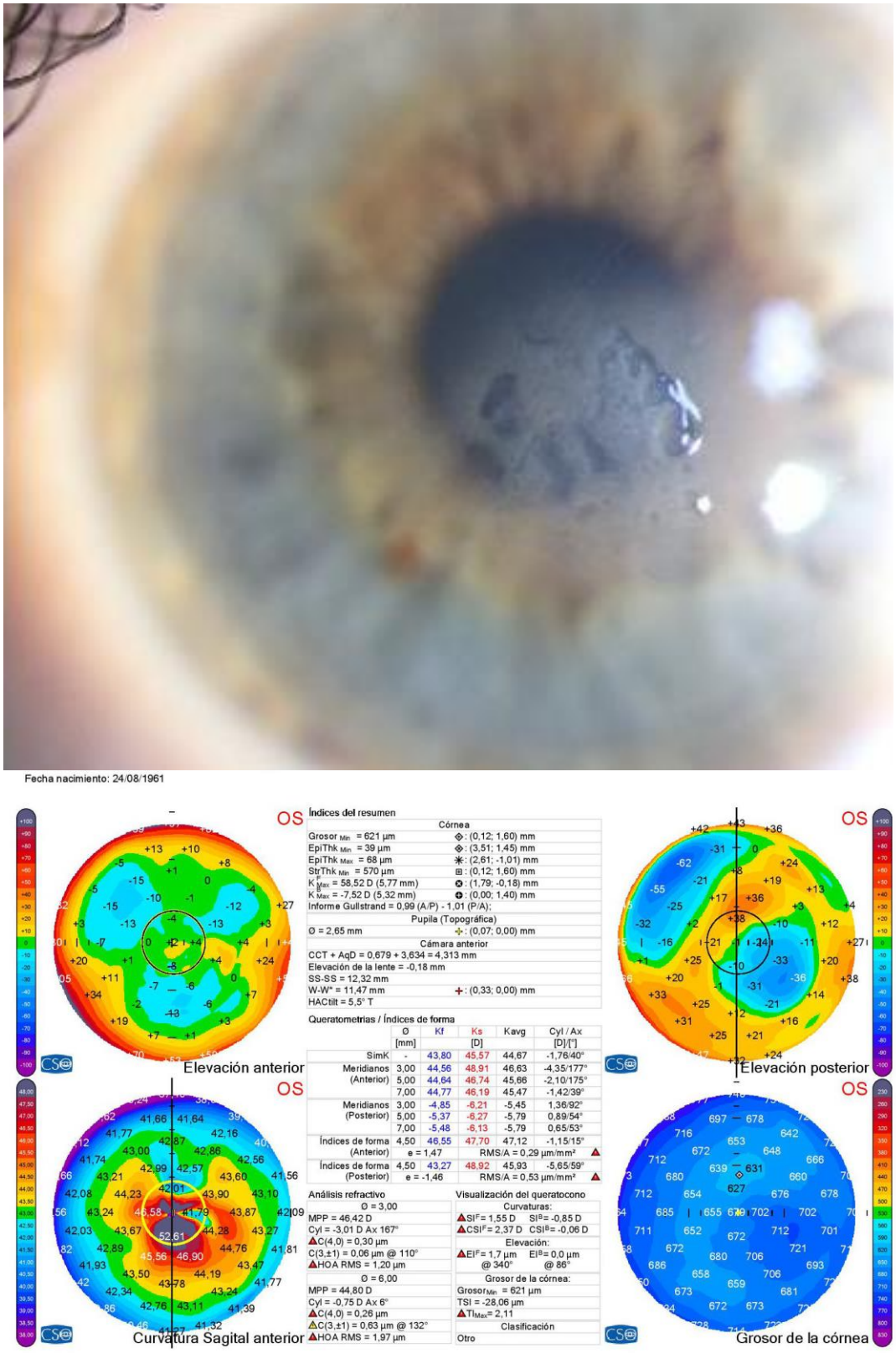


Figure 8. Anterior segment photograph of a patient with advanced stage, late-onset Fuchs' endothelial corneal dystrophy, with epithelial bullae, significant stromal oedema, and Descemet's membrane thickening. Corneal tomography (MS-39, CSO) showing significant corneal thickening in the pachymetry map as well as issues with keratometry.

After DMEK, the posterior corneal radius (PRC) is expected to change at a larger magnitude than the anterior corneal radius (ARC), leading to changes in total corneal refractive power contributing to the hyperopic shift.[39-42] In triple DMEK surgery or in sequential CE then DMEK surgery, IOL constant optimization and incorporating corneal topographic/tomographic parameters, including asphericity, central-peripheral thickness relationship, corneal power modifications, and corneal posterior curvature and ratios of posterior and anterior curvature radii into IOL power determination may improve refractive results after DMEK.[39-43] Recently it has been suggested that distinguishing between intraocular lens calculation errors (DICE), also reported in some studies as refractive spherical equivalent shift (RSES) and DMEK-induced refractive shift (DIRS) may improve the interpretation of "hyperopic shifts" among researchers and clinicians, where DIRS is defined as the difference between 3-mm zone total corneal refractive power before and after DMEK, and DICE as the difference between refraction predicted by the Haigis formula using pre-DMEK biometric data and the real post-DMEK refractive outcome. Positive DIRS is associated with an increase in the PRC/ARC ratio and increased posterior q-value, whereas a hyperopic DICE is more associated with unexpected increases in ARC and decreases in the PRC/ARC ratio. Using the pre-DMEK ARC measured with a Scheimpflug device rather than with a biometer may reduce the occurrence of DICE.[44] Using the refractive shift of the first eye may predict the outcome for the second eye, in cases of bilateral triple DMEK surgery, with good predictability with good interocular refractive differences in 80% of patients.[45]

In eyes undergoing sequential surgery (CE plus IOL implantation, then DMEK) or in eyes undergoing triple surgery (CE plus IOL implantation plus EK), a novel, attractive option is the use of light-adjustable IOLs (Light Adjustable Lens (LAL, RxSight)), which can theoretically correct up to 2.00 D of residual sphere and up to 3.00 D (diopters) of cylinder.[446]

During CE surgery (+/- simultaneous EK), certain aspects are important in eyes with FECD. Wound construction during CE surgery should ensure water tightness; posterior corneal or limbal incisions are preferable, and some surgeons prefer the creation of scleral tunnels. We recommend the soft-shell technique to protect the corneal endothelium in cases of standalone CE, using dispersive OVD to protect the endothelium and cohesive OVD for space formation. Phacoemulsification parameters should be lowered in eyes with FECD, including lower infusion (lower bottle height), lower vacuum and flow rates. Phacoemulsification techniques with lower energy should be used, including the phaco-

rolling technique, and the use of “pulse-wave power” and “torsional phaco” rather than continuous-wave power. It is unclear whether femtosecond laser-assisted cataract surgery has a benefit in terms of endothelial cell damage over conventional phacoemulsification surgery. The infusion should be directed towards the iris rather than towards the endothelium, to decrease endothelial cell damage. Thorough removal of OVD is warranted regardless of whether EK is performed simultaneously, to reduce the risk of postoperative IOP rises that can be injurious to the corneal endothelium. Wound closure with stromal hydration should be gentle, avoiding exaggerated hydration which can compromise the corneal transparency of an already dysfunctional endothelium; the threshold for suturing the incision should be low in the setting of FECD. In the setting of triple EK surgery (CE + IOL implantation + EK, Figure 9), after phacoemulsification and IOL implantation, we recommend the use of intracameral miotics prior to performing the EK, to reduce the gas-IOL contact (reducing the risk of IOL opacification) and to prevent the gas endotamponade from escaping to the posterior chamber. After that, EK can be performed as described elsewhere;[47,48] descemetorhexis can be performed both under air infusion or using viscoelastic.

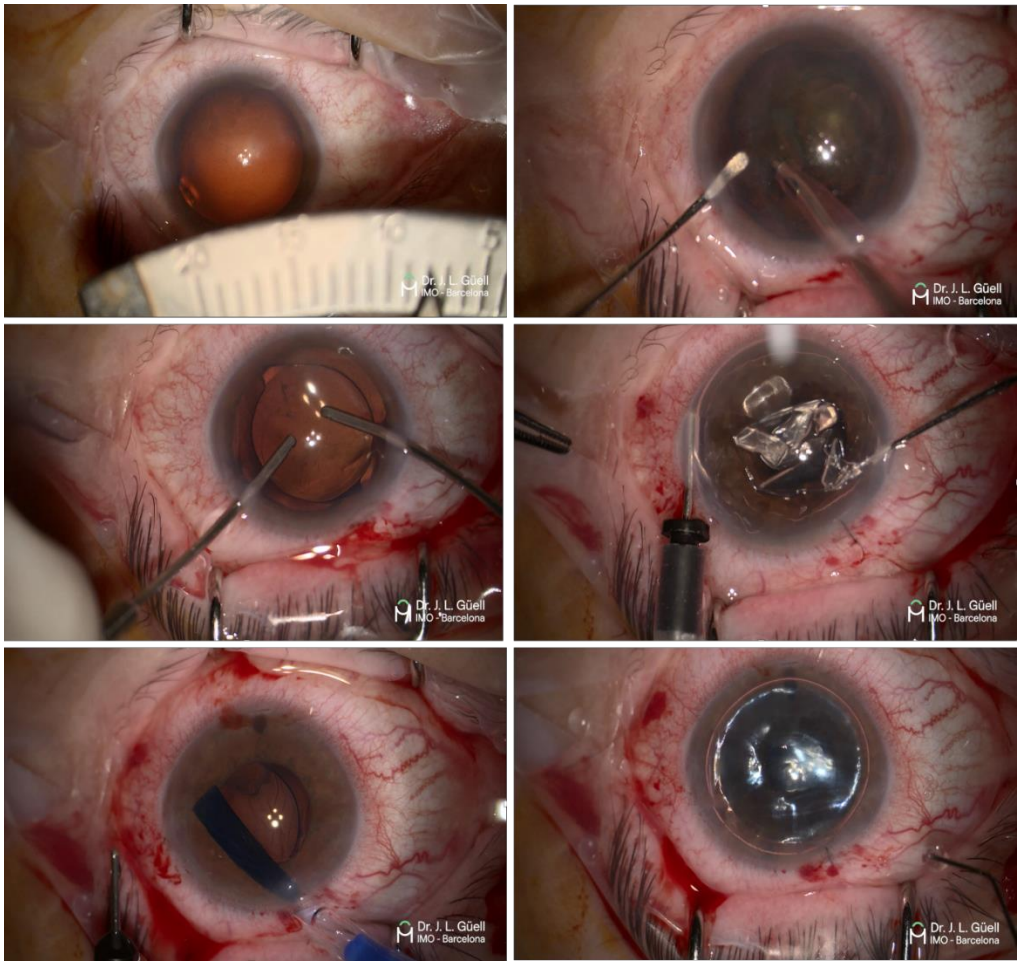


Figure 9. Triple DMEK surgery in a case of Fuchs' endothelial corneal dystrophy. It is important to use miotics after IOL implantation and before starting the DMEK procedure. Likewise, it is important to ensure that all viscoelastic is removed from the eye before DMEK graft insertion.

Resolution of corneal oedema after DMEK may be associated with a thinner-than-normal central cornea, steeper pachymetric progression from the thinnest point to the periphery, and higher posterior elevation values,[49] and so an enhancement after DMEK should be postponed until refractive and topographic stability is confirmed. The decision to perform a refractive enhancement should be made on a patient-by-patient basis. Successful excimer Laser keratorefractive enhancement has been reported in both DSAEK and DMEK.[50-53]

Increasing interest has been placed in phakic DMEK, with the main advantages being to preserve the crystalline lens in younger patients without cataract and the possibility to perform CE plus IOL implantation after the DMEK induced corneal deturgescence takes place, which allows to increase the refractive accuracy. Reported rates of lens surgery

after phakic DMEK range between 13% and 40%, with a relatively low medium-term projection of CE in this setting.[54,55] A recent meta-analysis found a highly variable rate of cataract development in phakic eyes after DMEK, with a mean 9.3% but a range from 0.4-72%.[56] However, surgeons considering phakic DMEK must take into account that phacoemulsification may lead to significant endothelial cell damage, with reported endothelial cell loss rates ranging between 4 and 25%. One study reported 11% endothelial cell loss 6 months after CE in eyes that underwent phakic DMEK.[54] Use of miotics intraoperatively is recommended to protect the crystalline lens. Descemetorhexis should be performed using cohesive OVD to increase space reducing risk of lenticular touch, and then removed to improve graft adherence. When the graft is being unfolded with tapping techniques, the surgeon should avoid compressing the AC to prevent lenticular touch. Ocular endotamponade in this setting should probably be performed with air rather than SF6 20%, since SF6 may induce cataract. Nevertheless, phakic DMEK may have similar graft detachment rates compared with pseudophakic DMEK in FECD eyes.

Even taking into account topographic data and constant optimization, most recent series still confirm the relative refractive unpredictability of triple DMEK or sequential surgery, with less than half of the eyes within +/- 0.50 D of target refraction and with 20-30% of eyes being > 1.00 D of target refraction.[38-40] This has limited the use of premium IOLs in DMEK patients. However, the adoption of phakic DMEK followed by lens surgery may open way for premium IOLs in endothelial keratoplasty, including toric IOLs and presbyopia-correcting IOLs.[57]

In FECD eyes with presence of central guttata judged to be the main cause of visual symptoms, without corneal stromal oedema, with a clear peripheral cornea and a peripheral ECD > 1000 cells/mm^2 on confocal or specular microscopy, stripping of the Descemet's membrane alone without corneal allografting has risen considerable interest among corneal surgeons (Descemetorhexis without endothelial keratoplasty (DWEK) or Descemet stripping only (DSO)). In these cases, a 4-mm central descemetorhexis is performed, and the crystalline lens may be left in place or CE and IOL implantation may be performed simultaneously. Stripping of the Descemet membrane-endothelium complex is followed by centripetal migration of peripheral corneal endothelial cells, leading to improvement in vision, reduced symptoms related to corneal guttae, and reduced pachymetry.[58-60]

Specific ocular conditions

Keratoconus and corneal ectasia

In KC, ectasia tends to stabilize after the age of 40 years; in cases of unstable KC requiring CE, stabilization of the ectatic cornea with corneal crosslinking (CXL) must be considered before performing CE. The two main challenges in patients with KC undergoing CE may be broadly categorized as 1) challenges in IOL determination and 2) challenges with visual outcomes. A third issue is the infrequent (but not neglectable) association between KC and FECD,[61] and surgeons dealing with KC and cataract should include assessment of corneal endothelium morphology and function in their routine preoperative assessment. One study of 25 eyes with stable KC and corneal endothelial dysfunction found that DMEK is safe and effective, with good visual and refractive outcomes and corneal flattening.[62]

The challenges in IOL determination include issues with keratometry, keratometric refractive index of the cornea, mismatch between the steepest area of the cornea and the visual axis, the determination of axial length, the posterior corneal curvature, the presence of corneal high-order aberrations, and the instability and unpredictability of after the wound creation for cataract surgery. Contact lens wearers must be instructed to cease contact lens (CL) wear before the preoperative evaluation to ensure adequate determination of manifest refraction, keratometry and biometric measurements. We typically recommend one week of CL abstinence in soft CL wearers, and 3 weeks of CL abstinence in RGPCL wearers.

The irregular corneal shape in KC makes keratometry readings difficult to obtain and use. Keratometry assumes a degree of consistency in corneal curvature along any given meridian, and this assumption is lost in KC eyes which have asymmetrical corneal curvatures. The standard keratometric refractive index of 1.3375 assumes a normal ratio between the anterior and posterior corneal surfaces, but this is disrupted in KC. Finally, increased corneal curvature, axial length and anterior chamber depth typical of KC eyes and the abnormal relationships between these morphometric parameters limit the applicability of standard formulas to predict the effective lens position. All these aspects lead to a typical overestimation of corneal power, leading to an underestimation of IOL power with consequent postoperative hyperopia, and this refractive unpredictability of CE in KC eyes is increased in more advanced KC compared with mild and moderate KC. It has been proposed that SRK/T (Sanders Retzlaff Kraff/Theoretical) formula may yield the best refractive accuracy in KC eyes, and newer formulas such as the Kane-KC formula may further improve accuracy (the Kane-KC formula is available online at https://www.iolformula.com).[63] We recommend using multiple IOL formulas in KC eyes undergoing CE, usually Haigis plus

SRK/T plus Barrett Universal II; we have also started using the Kane-KC online formula (*unpublished data*). Importantly, we recommend adjustments to the refractive target according to the keratometry/stage: for eyes with <48.00 D no adjustment; for eyes with 48-53 D, a target of -0.75 to -1.50 D; and for eyes with >53.00 D, a target of -2.00 to -3.00 D. Since most KC patients are myopic, it is wise to err on the myopic side and not overcorrect, to reduce risk of dissatisfaction.

In KC eyes with significant irregular astigmatism, a monofocal spherical IOL may be the best indication after CE, although visual outcomes will be limited by the presence of irregular astigmatism and RGPCL wear will still be needed after CE. Toric IOLs may be considered in mild to moderate, non-progressive KC, with good historical visual acuity not dependent of RGPCL, absence of significant irregular astigmatism in the central 4-mm, and in eyes where the keratometric astigmatism axis matches the manifest cylinder axis.[64] Of note, we may also consider toric IOLs in other keratoconic eyes with some irregular astigmatism, but the patient will need to understand that these IOLs will only be able to correct the regular component of the astigmatism and not the irregular one. In these eyes with significant irregularity, there is potential for pinhole-aperture IOLs (e.g., XtraFocus lens, Morcher; IC-8,AcuFocus, Inc.). The XtraFocus is an add-on lens without optical power which has been implanted in eyes with significant corneal irregularity.[65,66] The IC-8 IOL is an enhanced depth-of-focus IOL, but it has also shown to significantly improve corrected distance visual acuity as well as near and intermediate vision in KC eyes with significant irregularity, with high satisfaction rate.[67] One additional option is to implant a spherical IOL and later address the cylinder error with a "piggyback" IOL, as in post-PKP eyes undergoing cataract surgery.

Some surgical peculiarities apply in KC eyes. Smaller incisions should be constructed, to decrease the amount of surgically induced astigmatism. Clear corneal incisions should be made as close to the limbus as possible, and some surgeons prefer making modified scleral tunnels. Scarring and irregularities of the KC cornea can cause light scattering during CE surgery, and using a dispersive OVD over the cornea (e.g., hydroxypropyl methylcellulose 2%) improves hydration of the epithelium and provides some magnification of the intraocular contents for the surgeon. The surgeon should adjust phacoemulsification parameters to stabilize the deep AC of KC eyes, by lowering inflow pressure and thus decreasing intraoperative IOP and so limiting the stress on the ectatic cornea. Because KC eyes may have reduced healing capacity, a lower threshold for suturing of the clear corneal incisions should be adopted at the end of surgery.

Pellucid marginal degeneration (PMD) is another primary corneal ectasia, characterized by ectasia just above the area of corneal thinning typically involving the inferior cornea, concentric with the limbus, between the 4 and 8 o'clock meridians, and leading to highly irregular, against-the-rule astigmatism with the typical "crab-claw appearance" in corneal power maps illustrating the shift in astigmatism from the superior to inferior cornea. Structural interventions in eyes with PMD and significant thinning include CXL and partial- or full-thickness techniques. In patients with PMD and concurrent cataract, traditionally treatment consisted of combined penetrating keratoplasty plus CE and IOL implantation. However, more recently some authors have proposed that these cases may be managed with combined CE and inferior wedge resection keratectomy,[68] and good results have been observed with hydrophobic toric IOLs, which may even be superior to those in KC. It may be due to the good regularity of the central part of the cornea in comparison with KC.[69] For eyes with higher levels of astigmatism, customized toric IOLs may also be effective.[70]

Salzmann nodular degeneration and pterygium

Salzmann nodular degeneration (SND) is a relatively common corneal degeneration, characterized by the appearance of greyish-white, elevated nodules evident on slit-lamp examination, typically in a peripheral location although they can occur anywhere on the cornea. Patients with SND may be asymptomatic or report foreign body sensation, and in some cases blur to the irregular astigmatism. Placido-disc topography mires appear distorted, usually causing central flattening and astigmatism. Strategies to treat Salzmann's nodules include surgical nodulectomy / superficial keratectomy (with or without adjuvant alcohol or mitomycin C), and phototherapeutic keratectomy (PTK).

We recommend that SND be addressed before cataract surgery in order to properly calculate IOL power and alignment. One study of cataractous eyes with SND found that optical-biometer keratometry measurements changed significantly in nearly all cases after superficial keratectomy or PTK, with implications in the recommended IOL toricity.[71] The same considerations apply in the case of pterygia, since pterygia extending for more than 2mm into the cornea and pterygia with wider areas induce more than 0.50 D in IOL power calculations.[72]

Inflammatory ocular surface disease

Greater care must be exercised in the timing and surgical planning of patients with severe, inflammatory ocular surface disease. Cataract surgery is known to exacerbate ocular surface and dry eye disease, increasing the risk of corneal infection, reactivation of inflammatory disease, or corneal melt. Although aggressive lubrication can be sufficient to prevent complications in some conditions and in milder forms of disease, ensuring the disease is well controlled and quiet prior to operating is fundamental and may require topical steroids or cyclosporine, and may even require systemic immunosuppressive therapy to avoid serious complications. Furthermore, careful planning of the wound location may help to avoid triggering an exacerbation of disease. Finally, minimizing postoperative topical medications avoids the toxicity of preservatives, and particularly non-steroidal anti-inflammatory drugs should be avoided if possible.[73]

Patients with a history of epithelial or stromal herpetic keratitis also require specific perioperative care. Although infrequent, recurrences of herpes simplex virus (HSV) keratitis have been reported following cataract surgery, with one recent study found a surprisingly high rate of postoperative keratitis or uveitis after cataract surgery (45%);[74] similar rates have been reported in the setting of herpes zoster keratitis and/or uveitis.[75] The preoperative evaluation should include assessment of history and clinical findings associated with HSV keratitis in order to initiate timely antiviral medications to prevent discomfort and further vision loss secondary to viral reactivation and secondary keratitis. Risk factors for recurrence of HED include higher number of recurrences prior to surgery, shorter quiescence prior to surgery, and presence of iris transillumination defect at preoperative assessment.[73] Although data supports the use of prophylactic oral antivirals in penetrating keratoplasty to reduce recurrence and graft rejection, no studies have examined the role of antivirals in preventing HSV recurrence after cataract surgery.[76] In eyes with history of stromal herpetic keratitis or herpetic uveitis, we recommend a quiescence period of at least 6 months after the recurrence episode, and we recommend oral antiviral prophylaxis with acyclovir 400 mg twice daily, or valacyclovir 500 mg once daily starting one month before surgery and kept until steroids are withdrawn.

Aniridia-related keratopathy and cataract

Aniridia is a pan-ophthalmic disease which may be associated with limbal stem cell deficiency, including corneal pannus and, chronic epithelial breakdown (aniridia-associated keratopathy); iris defects; progressive zonulopathy; cataract and friable anterior capsule; glaucoma; and optic nerve and foveal hypoplasia. Lack of iris anatomy and zonular instability

provide increased surgical challenges during CE. Placing the IOL may be challenging, and lack of iris tissue ; capsular tension rings may be required to stabilize the capsular bag. Strategies to correct iris defects include aniridia rings, aniridia IOLs, or custom-made artificial iris, where an IOL may be sutured.[77] Visual outcomes may be limited by concurrent amblyopia or optic nerve or foveal hypoplasia, by postoperative raises in intraocular pressure, and by decreased corneal graft survival. and patients may require limbal stem cell transplantation before keratoplasty to optimize the post-keratoplasty epithelial healing, or undergo simultaneous keratolimbal allograft plus keratoplasty; simultaneous keratolimbal allograft plus PKP may be associated with less favourable outcomes.[78]

Outcomes and complications

Penetrating keratoplasty and cataract

Triple PKP surgery is a well-established surgical option in eyes with coexisting corneal pathology and cataract, with most series reporting 40-70% of eyes reaching BCVA >20/40 and 60-90% graft survival rates over the medium-long term. The most common complications are as in standalone PKP, including glaucoma, allograft rejection, and continuous endothelial cell loss.[79-83] Whether refractive outcomes after triple PKP are inferior to those of "conventional" sequential surgery remains controversial , with 50-70% of eyes within 2.00 D of target refraction.[84,85] Performing PKP and CE surgery at one stage with secondary IOL implantation later significantly improves refractive outcomes, with nearly 90% of eyes within 2.00 D of target refraction and approximately half within 1.00 D of target refraction; a recent study has found a mean spherical equivalent of -0.19 D 6 months after secondary IOL implantation.[13] Risk factors for failure of triple PKP historically include intracapsular CE, postoperative complications, and additional surgeries.[8,86]

Anterior lamellar keratoplasty and cataract

Combined DALK and CE has very favourable visual outcomes, with a high proportion of cases reaching BCVA >20/60 (18 of 20 eyes in one case series),[17] and with a low risk of intraoperative or postoperative complications. Conversion to PKP is a risk, as in a standard DALK, and this risk is higher in cases of type 2 big bubble DALK, as previously discussed.[19]

Posterior lamellar keratoplasty and cataract

Most studies and meta-analyses have concluded that DMEK leads to earlier visual recovery, lower hyperopic refractive shift, better visual acuity, lower levels of higher-order

aberrations, and lower cumulative rejection rates compared with conventional DSEK/DSAEK, albeit a greater re-bubbling rate;[38,87,88] however, it remains uncertain that need of re-bubbling after DMEK affects outcomes adversely,[89] and re-bubbling rates after DMEK have decreased progressively, due to increased surgical experience, the use of sulfur hexafluoride 20% ocular endotamponade for graft attachment and adequate postoperative positioning.[47,48] Endothelial cell loss and graft survival are comparable after DMEK and DSAEK over the medium-long term, with reported 68-72% endothelial cell loss rates at 10 years,[90-92] and 80-95% cumulative graft survival rates after 5-10 years follow-up. DMEK rejection rates at 5-10 years are less than 4%,[90] in comparison to an average 10% of rejection after DSAEK. Visual outcomes and graft survival are more comparable between DMEK and ultrathin DSAEK (UT-DSAEK). However, two randomized controlled trials concluded that DMEK eyes tend to reach higher levels of visual acuity,[93,94] and that DMEK is associated with less higher-order aberrations than UT-DSAEK.[95] Besides, UT-DSAEK has a higher rejection rate, with reported rates of 7% at 5-year follow-up,[96] compared with 2.6% rates at 5 years and 4% at 10 years after DMEK.[90,97] The high efficacy and safety profiles of DMEK are reflected in the continuously increasing trends in the USA, where the number of DMEKs have now matched the number of DSAEKs, in stark contrast with the data in the previous decade.[28]

Outcomes of combined CE and DMEK suggest that visual outcomes after triple DMEK surgery are comparable to those of sequential surgery (phacoemulsification followed by DMEK), that triple DMEK may be associated with superior refractive outcomes, but possibly at the cost of higher re-bubbling rates,[98,99] although this has been disputed by some authors.[55,100,101] Similarly, it is still controversial whether endothelial cell loss is greater after triple DMEK compared with sequential surgery.[102,103] It has been suggested that sequential surgery may have lower risk of postoperative cystoid macular edema compared with triple DMEK or with standalone DMEK in previously pseudophakic eyes (*Moura-Coelho N., Güell JL., paper under review*), suggesting that topical non-steroidal anti-inflammatory drugs may be protective.[104,105]

Descemetorhexis without endothelial keratoplasty, Descemet's stripping only and cataract

Twelve-month results have been promising in eyes undergoing DWEK/DSO, with significant improvements in unaided and corrected distance visual acuity.[59] Only two studies have analysed longer follow-up data (total of 6 eyes), with one case of primary failure at the early postoperative period and another eye developing corneal decompensation 1 year after

DSO; 4 eyes had stable improvements in visual acuity (mean 0.18 logMAR, range 0.3-0.0 logMAR) and corneal thickness.[106,107] One study found that combined phaco-DWEK induced approximately 0.50 D hyperopic shift, which should be considered for IOL selection if CE surgery is performed; in this study, 92% of eyes were within 1.00 D of target refraction but only 48% were within 0.50 D of the target refraction.[108] The time to visual recovery after DWEK/DSO is usually longer than that after DMEK, with studies reporting a mean time to visual recovery of 7.1 weeks.[109] Early use of Rho kinase inhibitors after DWEK/DSO may significantly reduce the time to corneal clearance after surgery and lead to increased endothelial cell counts,[110] and for many of us it is a necessary co-adjuvant tool in DWEK surgery. A recent systematic review and meta-analysis of DWEK/DSO including 127 eyes from 11 articles concluded that a descemetorhexis (with or without Rho kinase inhibitors) ≤4 mm improved visual acuity and reduced corneal central thickness, with a 4% rate of failure of the surgery with need of an EK graft. This was in contrast with eyes where descemetorhexis was larger than 4 mm, where visual and anatomical benefits were not found, implying a significantly higher rate of failure.[60]

Conclusions

The decision-making process in combined cataract and corneal disease (Figure 10) requires a thorough history taking and clinical examination, taking into account patient characteristics and aspects such as speed of visual rehabilitation, intraoperative complications, and management of postoperative complications such as EK graft detachment requiring re-bubbling or IOP rises and significant postoperative inflammation leading to endothelial cell damage. Surgeons need to be trained in the different surgical strategies of both full thickness and lamellar transplantation combined with CE surgery, in order to fulfil patient and surgeon's increasing demands for earlier, sustained, and improved final visual and refractive outcomes. However, some aspects regarding improved refractive accuracy after keratoplasty and CE still require long term follow-up efficacy and safety data, including eyes undergoing CE and DMEK, secondary IOL and piggyback IOL implantation after PKP and DALK, the use of LALs in keratoplasty eyes, and the DWEK/DSO.

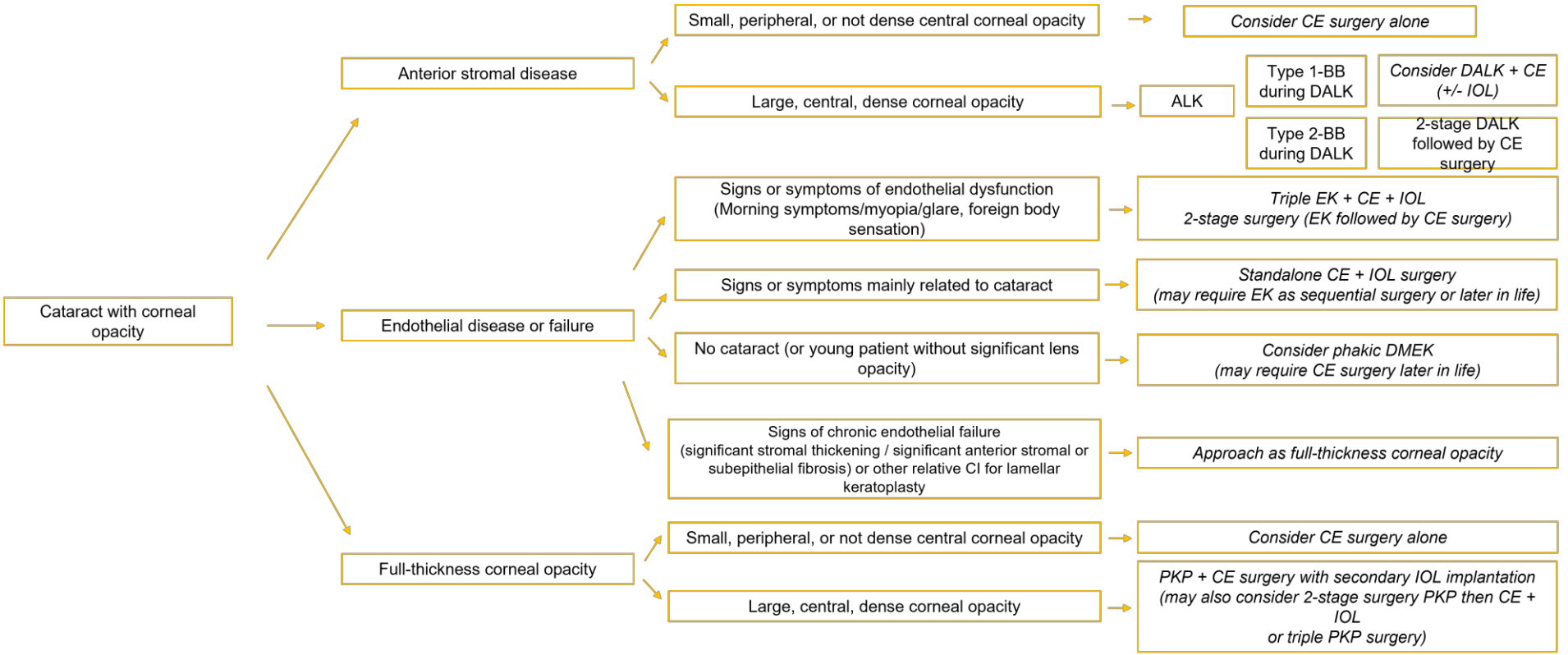


Figure 10. Decision flowchart in patients with cataract and corneal opacities. *CE* – cataract extraction; *ALK* – anterior lamellar keratoplasty; *BB* – big-bubble; *DALK* – deep anterior lamellar keratoplasty; *IOL* – intraocular lens; EK – endothelial keratoplasty; DMEK – Descemet's membrane endothelial keratoplasty; CI – contraindications; PKP – penetrating keratoplasty

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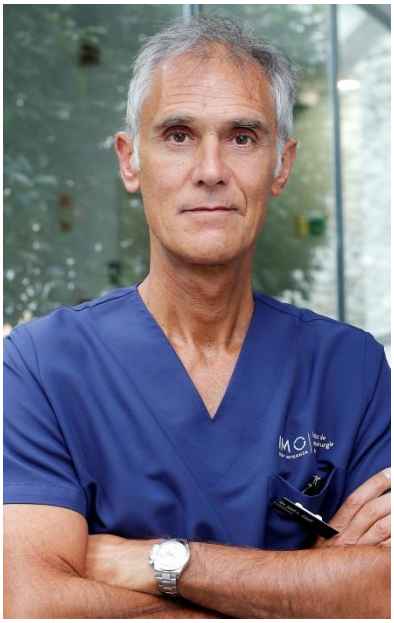
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Módulo 8. Distrofias corneales

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Resumen (15 líneas)

Las distrofías corneales son un grupo heterogeno de enfermedades corneales hereditárias, habitualmente bilaterales, simétricas y progresivas; sin embargo, hay excepciones para cada parte de esta definición. Se clasifican según la capa corneal primariamente afectada y considerando también la genética. De un modo general, son enfermedades raras, con excepciones notables la distrofia de membrana basal epitelial y la distrofia endotelial de Fuchs. Las distrofías epiteliales pueden ser asintomáticas o manifestarse con erosiones corneales recurrentes (ECRs), con fotofobia, lagrimeo y afectación visual. Las distrofías de la capa de Bowman se caracterizan por la aparición de opacidades e irregularidad corneal, causando ECRs y afectación visual importante. Las distrofías estromales son clínicamente heterogeneas y pueden ser asintomaáticas o afectar la visión. Las distrofias endoteliales pueden llevar a la aparición de edema corneal y disfunción visual. El tratamiento de las distrofías corneales incluye técnicas para el tratamiento de las ECRs y técnicas para rehabilitación visual. La queratectomía fototerapéutica y la queratoplastía son las dos principales estratégicas para rehabilitación visual en estas enfermedades, sin embargo se observa una elevada tasa de recurrencias. Las nuevas terapías celulares y genéticas podrán retrasar o curar algunas de estas enfermedades.

Puntos clave (máx 10 frases)

1. La definición de distrofia corneal incluye los conceptos de hereditariedad, bilateralidad, simetria y progresión de la enfermedad. Sin embargo, existen excepctiones para cada parte de esta definición.
2. Con excepción de la distrofia de membrana basal epitelial y de la distrofia endotelial de Fuchs de início tardio, las distrofias corneales son enfermedades raras.
3. Actualmente las distrofias corneales se clasifican según la anatomía pero también teniendo en cuenta los aspectos genéticos de la enfermedad, utilizándose la clasificación del *International Committee for Classification of Corneal Dystrophies* (IC3D) revisada en 2015.
4. Las distrofías epiteliales pueden ser asintomáticas o presentarse con erosiones corneales recurrentes, fotofobia, lagrimeo o disminución de la visión. Su tratamiento está indicado cuando provocan síntomas o erosiones corneales recurrentes.
5. Las distrofias de la capa de Bowman son relacionadas con el gen *TGFB1*; en los estadios iniciales, las distrofías de Reis-Bücklers y de Thiel-Behnke pueden confundirse ya que comparten aspectos genéticos, moleculares y clínicas, con la aparición de opacidades e irregularidad corneal con afectación visual importante. La queratectomia fototerapéutica (PTK) y la queratoplastía tienen elevada efectividad en estas distrofias, pero recurrencias frecuentes.
6. Las distrofías estromales son un grupo heterógeno de enfermedades que habitualmente consisten en la aparición de opacidades estromales que pueden o no afectar la visión.
7. La distrofia endotelial de Fuchs tiene una variante rara de ínicio precoz y una variante de início tardio muy prevalente, afectando principalmente mujeres a partir de la quinta década de vida.
8. La PTK con láser de excimer está indicada en pacientes con ECRs y/o con opacidades anteriores con afectación visual; es altamente efectiva y se pueden realizar retratamientos en casos con opacidades recurrentes.
9. La queratoplastia está indicada en distrofias con afectación visual importante; las técnicas de queratoplastía lamelar (anterior y posterior) se asocian a pronósticos visuales comparables a la queratoplastia penetrante y presentan un perfil de seguridad y de rechazo más favorable.
10. La terapía genética y las terapías celulares podrán tener un papel importante en el tratamiento de las distrofias corneales.

Objetivos didácticos

En este módulo, se pretende que los alumnos adquieran la capacidad de identificar las distrofías corneales a partir de su aspecto clínico por biomicroscopía por lámapara de hendidura, con enfoque particular a la distincción entre las diferentes distrofias corneales y principalmente la formulación de correcto diagnóstico diferencial con otras entidades nosológicas sistémicas y puramente oftalmológicas. Se pretende también que los alumnos adquiran un conocimento más aprofundado de los aspectos patológicos, moleculares y genéticos de estas enfermedades, así como de la pluralidad de herramientas de diagnóstico por imagen que auxilian el diagnóstico clínico, sobre todo en los casos clínicos de mayor dificultad diagnóstica. Finalmente, se pretende que los alumnos adquieran la capacidad de decisión clínica y terapétuca en estos casos, con enfoque particular para las indicaciones para queratectomía fototerapéutica y queratoplastía. Se pretende también que los alumnos tengan una actualización sobre las terapéuticas emergentes para estas enfermedades, en particular para la distrofía endotelial de Fuchs y para algunas distrofías con mutación genética conocida.

1. INTRODUCCIÓN

La palabra "distrofia" es derivada del griego "dys" (incorrecto) y "trophe" (nutrición"), y la expresión "distrofia corneal" fue descrita por primera vez en 1890 por Arthur Groenouw, donde describió dos casos de distrofias corneales estromales. Las distrofias corneales son un grupo de enfermedades corneales hereditárias, habitualmente bilaterales, simétricas, progresivas (pero de progresión variable según la enfermedad específica), y no relacionadas con factores ambientales o sistémicos; y que pueden afectar cualquier capa de la córnea. Sin embargo, hay excepciones para cada parte de esta definición: la mayor parte de los pacientes con distrofia de membrana basal epitelial (EMBD, del inglés *epithelial basement membrane dystrophy*) no tiene un patrón hereditário; algunos pacientes con distrofia corneal polimorfa posterior (PPCD, del inglés *posterior polymorphous corneal dystrophy*) tienen alteraciones unilaterales y puede no ser progresiva; y pacientes con distrofia macular pueden tener alteraciones sistémicas, con alteraciones de de los niveles de queratano sulfato (KS, del inglés *keratan sulphate*) en el suero.

1.1. Clasificación de las distrofias corneales

Historicamente, se han clasificado las distrofias corneales según su morfología. Sin embargo, este sistema ha presentado múltiples limitaciones. Las enfermedades degenerativas de la córnea son un grupo de enfermedades caracterizadas por alteraciones corneales resultantes del envejecimiento y/o de traumatismos de repetición, y su aspecto puede confundirse con el de una distrofia corneal. Por otro lado, históricamente se describieron muchas "distrofias nuevas" que actualmente se saben tratarse de variantes de alguna distrofía ya anteriormente descrita. Actualmente, la clasificación de las distrofias de la *International Committee for Classification of Corneal Dystrophies* (IC3D) revisada en 2015 sigue siendo basada en la anatomía, según la capa corneal principalmente afectada, pero incluye aspectos de la genética; cada distrofia es descrita según el nível de evidencia científica disponible según categorias 1 a 4 (Weiss et al. Cornea 2015):

- Categoria 1: Distrofia corneal bien definida donde el gen ha sido mapeada y se conocen mutaciones específicas del gen (por ejemplo: distrofia de Thiel-Behnke)
- Categoria 2: Distrofia corneal bien definida que ha sido mapeada para uno o más *loci* cromosomales específicos, pero sin identificación del gen (por ejemplo: distrofia de endotélio corneal relacionada con el cromosoma X)
- Categoria 3: Distrofia cornela bien definida pero no mapeada a ningún *locus* cromosomal (por ejemplo: distrofia corneal de Francheschetti)
- Categoria 4: Casos de sospecha de nuevo tipo de distrofia corneal o de distrofia corneal ya previamente documentada, donde la evidencia de que se tratan de una entidad clínica distinta todavía no es convincente (por ejemplo: distrofia corneal central de François).

1.2. Epidemiologia

Aparte de la EMBD y de la FECD, las distrofias corneales son raras en la población. La prevalencia de las distrofias no está definitivamente caracterizada, con frecuencias estimadas variables según el tipo de distrofia, la población estudiada y posiblemente la localización geográfica. La EBMD es la distrofia corneal más frecuente, pero su prevalencia depende de los métodos diagnósticos utilizados. Un estudio de 1981 reportó una prevalencia tan elevada como del 42% de la población de los Estados Unidos; sin embargo, es posible que la prevalencia real sea más elevada con la evolución de los métodos de imagen y consecuente detección de la EMBD en sujetos asintomáticos. La prevalencia global estimada de la FECD es de un 7.3% (intervalo de confianza de 95% = 4.1-12.8%) , según un meta-análisis global reciente (Aiello et al. J Ophthalmol, 2022). Se estima que la prevalencia de la distrofia corneal granular tipo 2 (GCD2, del inglés *granular corneal dystrophy type 2*) es de 8-11 casos por 10.000 personas en Korea y de 8 casos por cada 10.000 personas en Estados Unidos. La distrofía corneal *lattice* tipo 1 (LCD1, del inglés *lattice corneal dystrophy type 1*) tiene una prevalencia estimada de 11 casos por 10.000 personas en los Estados Unidos, según un estudio de dimensión nacional realizado pro un período de siete años en ese país. La mayor parte de las otras distrofias epiteliales, estromales y endoteliales son en general consideradas enfermedades raras con prevalencias inferiores a 1 por millón de personas, pero hay variaciones geográficas y étnicas importantes. Por ejemplo, en Japón se ha reportado una prevalencia de la distrofia gelatinosa (GDLD, del inglés *gelatinous drop-like corneal dystrophy*) de 1 en cada 33.000 personas, pero la GDLD es relativamente incomún en otros grupos étnicos. Finalmente, en grupos de personas con elevados niveles de consanguinedad o en zonas geográficas con fuerte influencia del efecto fundador, se observan prevalencias anormalmente elevadas de distrofías corneales. (Soh et al. Nat Rev Dis Primers, 2020).

2. DISTROFIAS CORNEALES ANTERIORES

Las distrofias corneales anteriores, o distrofias epiteliales y subepiteliales, incluyen enfermedades que afectan sólo el epitelio, el epitelio y su membrana basal (MB), o la capa de Bowman (BL, del inglés *Bowman layer*). Las distrofias de la BL habitualmente presentan alteraciones patológicas del estroma adyacente así como del epitelio y su MB. Pueden ser asintomáticas; típicamente, las distrofias corneales anteriores son sintomáticas y se presentan con erosiones corneales recurrentes (ECR) y/o con disminución de agudeza visual (AV) por astigmatismo irregular o opacidad corneal anterior.

2.1. DISTROFIAS EPITELIALES

2.1.1. Distrofía corneal de Meesmann (OMIM: 122100 618767)

La distrofia corneal de Meesmann (MECD, del inglés *Meesmann corneal dystrophy*) es una distrofia rara, bilateral y simétrica, con patrón hereditariedad autosómico dominante (AD) resultante de mutaciones de dos genes de la keratina corneal (*KRT3* o *KRT12*) (categoria 1 de la IC3D). Histopatológicamente, se observan las siguientes alteraciones: 1) el engrosamiento y desorganización del epitelio, con la presencia de quistes intraepiteliales llenos de detritos citoplasmáticos y nucleares; 2) engrosamiento de la MB epitelial; 3) acumulación de material granular y filamentario ("sustancia peculiar") en el citoplasma de las células epiteliales en microscopía electrónica de trasmisión.

Habitualmente se presenta en la infancia y de modo asintomático, caracterizándose pela presencia de microquistes intraepiteliales o vesículas epiteliales visibles por biomicroscopía por lámpara de hendidura (BMC-LH), y que no suelen afectar significativamente la visión. Estas alteraciones ocurren en el eje visual y en la média periferia corneal, pero es rara la afetación de la perifería corneal. Son mejor visibles por retroiluminación o con iluminación indirecta en el íris. Los síntomas son infrecuentes y pueden incluir disminución de AV y sensación de cuerpo extraño o fotofobia.

2.1.2. Distrofia corneal epitelial de Lisch (OMIM 300778)

La distrofía corneal epitelial de Lisch (LECD, del inglés *Lisch Epithelial Corneal Dystrophy*) es una distrofia corneal rara bilateral, caracterizada por la presencia de opacidades epiteliales grises en múltiples patrones (en banda, en remolino, en llama, o con aspecto plumoso) que por retroiluminación se demuestra que consisten en quistes epiteliales densos. Se han descrito casos esporádicos y casos familiares de LECD; los casos familiares tienen patrón hereditario asociado ao cromosoma X dominante (XLD) en el *locus* Xp22.3, pero el gen no se encuentra todavía identificado (categoría 2 de la IC3D). El hallazgo principal en histopatología es la vacuolización difusa del citoplasma de las células epiteliales, principalmente en la capa epitelial alada, y con demarcación evidente entre áreas afectadas y áreas no afectadas del epitélio corneal. Estos vacúolos aparentan estar vacios cuando evaluados por microscopía electrónica. La LECD suele ser asintomática excepto si la opacidad epitelial afecta el eje visual, cuando puede presentar disminución leve, indolor y lentamente progresiva de la AV.

2.1.3. Distrofia corneal gelatinosa *"drop-like"* (OMIM 204870)

La GDLD es una distrofia corneal rara que se presenta habitualmente en la primera o segunda décadas de vida y que resulta de una mutación autosómica recesiva (AR) en el gen *TACSTD2* (categoria 1 de la IC3D). Se caracteriza por la presencia de lesiones epiteliales y subepiteliales

similares a la queratopatía en banda, podiendo también manifestarse en patrón de mora (pequeños grupos de múltiplos nódulos). Son lesiones hiperpermeables y que pueden teñir con fluoresceína a pesar de presentar el epitélio corneal íntegro.

En histología, se observan depósitos subepiteliales y estromales de amilóide, con coloración con rojo del Congo y con birefringencia a la luz polarizada.

Estos pacientes habitualmente presentan una disminución importante de la AV, así como síntomas de discomfort, fotofobía y lagrimeo. Esta enfermedad suele recurrer tras los tratamientos (discutidos más adelante en la sección de tratamiento) así como en los ojos que requieren queratoplastía para rehabilitación visual (Figura 1).

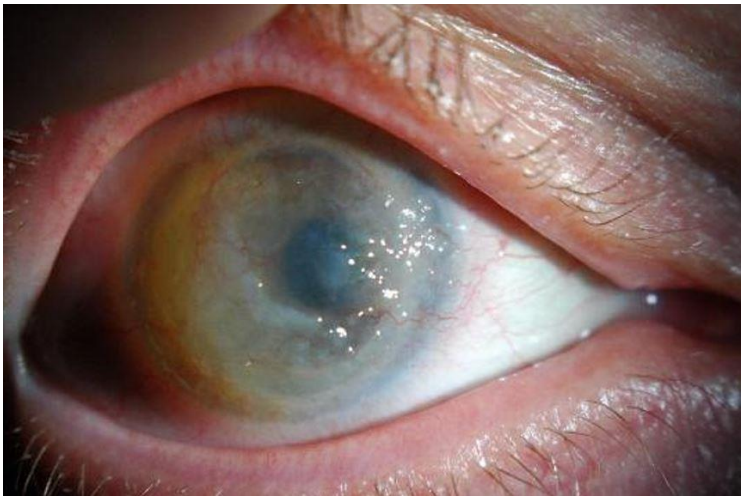


Figura 1 – Recurrencia de distrofia corneal gelatinosa "*drop-like"* tras queratoplastía.

2.1.4. Distrofía de membrana basal epitelial

La EBMD es la distrofia corneal más común y se considera una distrofía corneal porque parece haber una tendencia familiar para la aparición de estas alteraciones. Sin embargo, la EBMD no tiene una base hereditaria en la mayor parte de los casos; en algunos casos, se ha identificado mutaciones en el gen *TGFB1* (categoría 1 de la IC3D) (Soh et al. Nat Rev Dis Primers, 2020). Esta distrofia ha tenido multiples designaciones, incluyendo distrofia microquística de Cogan y distrofia en mapa-punto-huella.

En histopatología, la EBMD se caracteriza por la presencia de extensiones anómalas de MB epitelial hacía el epitélio (aspecto de "mapa"), que atrapan las células epiteliales formando quistes ("puntos"). La presencia de lineas concentricas de MB engrosada corresponde clinicamente al patrón de "huellas".

Clínicamente, se observan lesiones con aspecto de microquistes, con patrón de huellas o con patrón de mapa; estas alteraciones epiteliales son mejor visibles por retroiluminación (Figura 2).

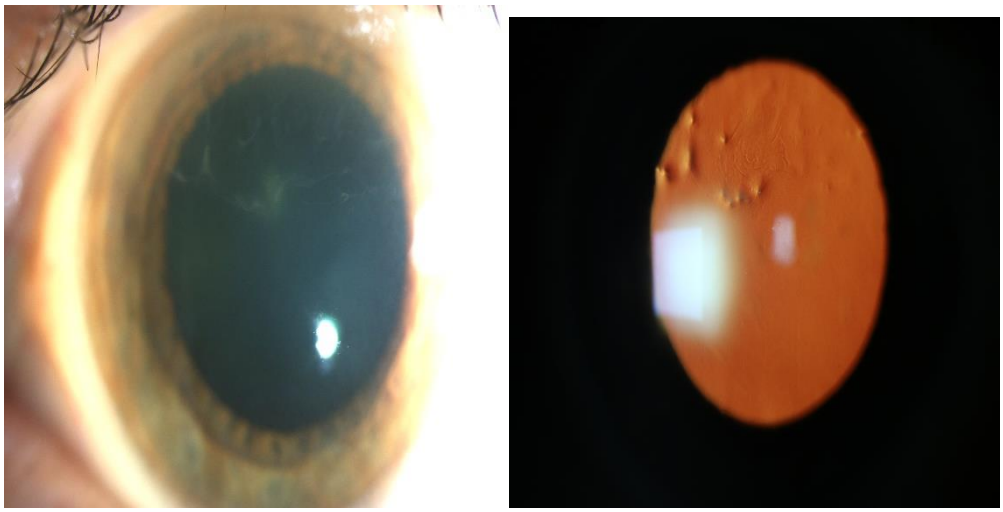


Figura 2 – Distrofia de membrana basal epitelial (A). Las alteraciones en aspecto de huellas son mejor apreciables por retroiluminación (B).

Las áreas afectadas pueden presentar el aspecto de "tinción negativa" con fluoresceína bajo la luz azul de cobalto. La EBMD es frecuentemente asintomática, pero los principales sintomas son ECRs espontáneas y visión borrosa con sensación de cuerpo extraño. Las erosiones corneales pueden ser leves y transitorias, durando minutos; un cuadro clínico relativamente frecuente es el del paciente que se presenta de urgencia por dolor espontáneo al despertar y abrir los ojos y al momento de la exploración oftalmológica no se encontrar hallazgos clínicos. La EBMD es responsable por un 25% de los casos de ECRs.

2.2. DISTROFIAS CORNEALES RELACIONADAS CON EL GEN *TGFB1*

El gen *TGFB1* codifica la proteína factor de crecimiento transformante beta-inducida (TGFBIp) o queratoepitelina, una proteína de 68 kDa de la matriz extracelular ubíqua en múltiples organos y sistemas como el corazón, hígado, páncreas, piel, hueso, tendones, riñon, endométrio y plasma sanguínea. (Han et al. Prog Ret Eye Res, 2016) En la córnea, la proteína se expresa sobre todo en el epitélio, en el estroma corneal en asociación con el colágeno tipo VI y en situaciones patológicas como la distrofia de Fuchs y en membranas fibrosas retrocorneales. La proteína TGFBIp es la segunda proteína más abundante del estroma corneal. Y sin embargo, el papel de la TGFBIp no es completamente conocido. Se piensa que tiene un papel fundamental en respuestas fisiológicas y patológicas al mediar la adherencia y migración celulares así como la proliferación y diferenciación celular.

Se ha identificado el gen *TGFB1* como causador de múltiples distrofias corneales, particularmente distrofias de la BL y distrofias del estroma anterior. Se han identificado más de 30 mutaciones

del gen asociadas a distrofias corneales, pero se reconocen dos "hot spots", los codones Arg124 y Arg555; la mutación más común identificada en algunos estudios ha sido la p.Arg124His. Las distrofias relacionadas con el gen *TGFB1* son clasificadas como categoría 1 de la IC3D e incluyen las distrofias de la BL y algunas distrofías del estroma anterior; notablemente, algunos casos de EBMD también se asocian a mutaciones de este gen.

2.2.1. DISTROFIAS DE LA CAPA DE BOWMAN

Las distrofias de la BL (categoria 1 de la IC3D) incluyen dos enfermidades que comparten muchos aspectos genéticos, moleculares y clínicos, la distrofia de Reis-Bücklers (RBCD, del inglés *Reis-Bücklers corneal dystrophy*) y la distrofia de Thiel-Behnke (TBCD, del inglés *Thiel-Behnke corneal dystrophy*). El aspecto clínico es similar sobre todo en las fases iniciales; la RBCD evoluciona de opacidades estromales anteriores e irregularidad corneal afectando la vision en edad pediatrica que se extenden hacía el limbo y posteriormente hacía el estroma, mientras que la TBCD tipicamente afecta la vision más tardiamente, empezando como opacidades punteadas que evolucionan para un patrón en havo de miel reticulado.

Histológicamente, las distrofias de la BL se caracterizan por la sustitucion del tejido normal por una capa fibrocelular; en la RBCD esa capa tiene una morfologia en banda y tiñe de rojo con tricromo de Masson, mientras que en la TBCD la capa tiene una configuracion en rueda dentada y la tinción con tricromo es variable y menos intensa. Ambas distrofias tienen carácter hereditario AD relacionado con el gen *TGFB1* en el locus 5q31. La mutación más frecuente en la RBCD es la p.Arg124Leu y en la TBCD es la p.Arg555Gln.

La RBCD se caracteriza por ECR y perdida visual secundaria a cicatricacion corneal desde la infancia. La TBCD se caracteriza por menor frecuencia de ECR y por pérdida visual más tardia. Ambas las distrofias tienen menos recurrencias de erosiones corneales con el aumento de la edad. La microscopia confocal *in vivo* (IVCM) puede permitir la distinción entre las dos enfermedades.

2.2.2. DISTROFIAS ESTROMALES RELACIONADAS CON EL GEN *TGFB1*

2.2.2.1. Distrofia corneal granular tipo 1 (GCD1, OMIM 121900)

La GCD1 es la forma clásica de la distrofia, como descrita inicialmente por Groenouw (distrofia de Groenouw). Es una distrofia AD caracterizada por la deposición de opacidades pequeñas bien delineadas grises-blanquecinas en el estroma central anterior que pueden tener forma de lágrima, forma de anillo o forma de migajas. Con la progresión de la distrofia, las lesiones individuales aumentan de dimensiones y de número y coalescen, extendiendose posteriormente en el estroma y hacia la periferia (Figura 3). La afectación de la visión habitualmente ocurre a partir de la quinta década de vida y resulta de la coalescencia de las opacidades corneales o de la opacificación del

estroma adyacente a los depósitos estromales. La sensibilidad corneal puede estar afectada en la GCD1. Las ECRs son infrecuentes en esta distrofia.

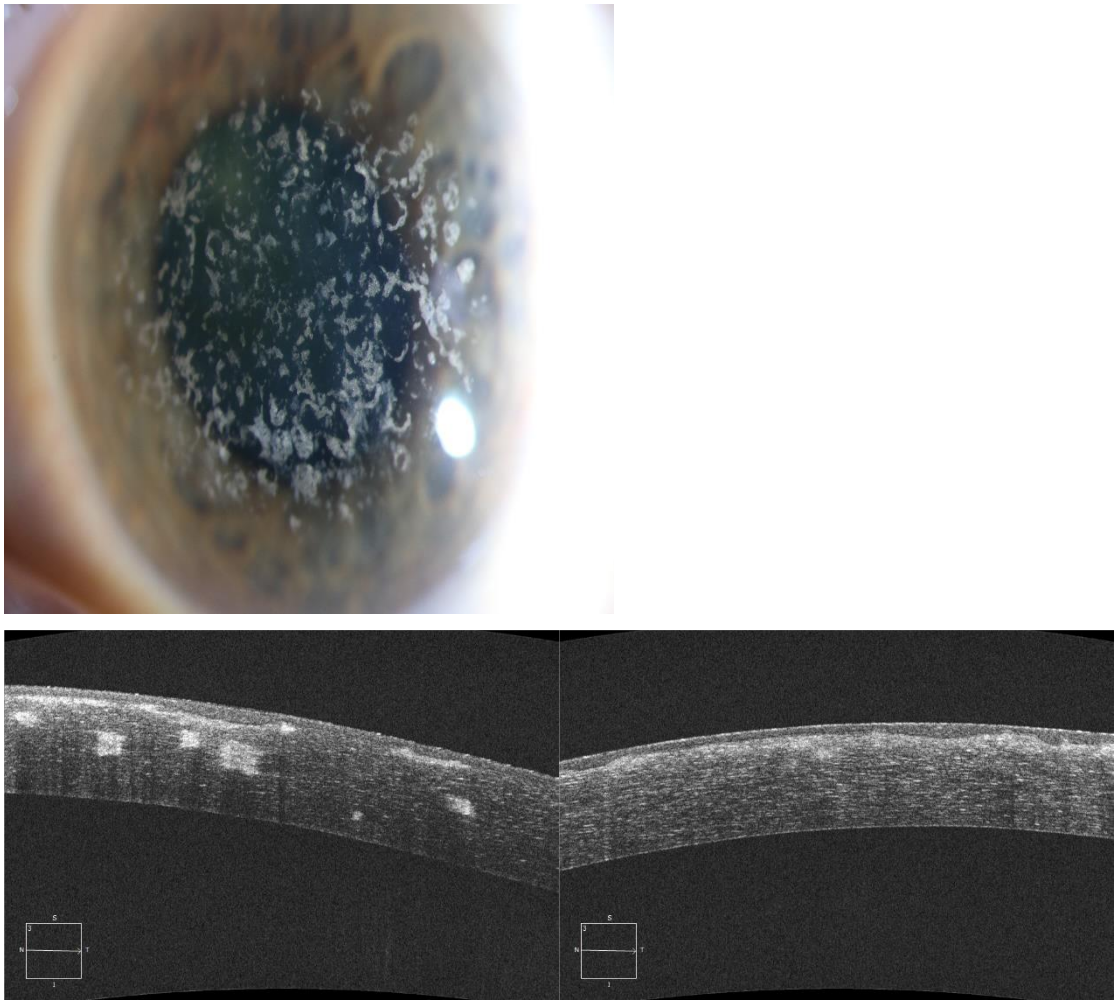


Figura 3 – Distrofia corneal granular tipo 1, con múltiples opacidades en el estroma central sobre todo en estroma anterior pero dispersos por todo el estroma corneal (A). En OCT-SA (B y C) se aprecian depósitos hiperreflectivos dispersos por todo el estroma corneal y que pueden provocar efecto de sombra para el estroma más profundo.

La histología de la GCD1 es típica, observándose depósitos extracelulares hialinos eosinofílicos subepiteliales y en el estroma que tiñen de rojo con tricromo de Masson y tiñen debilmente con *periodic acid-Schiff*. Resulta de una mutación relativamente conservada del gen *TGFB1* (mutación p.Arg555Trp).

2.2.2.2. Distrofia corneal granular tipo 2 (GCD2, OMIM 607541)

La GCD2 descrita por Avellino (distrofia de Avellino) es una variante de la distrofia granular caracterizada por opacidades granulares y tipo *lattice*. Holland y colaboradores han descrito los 3 signos clínicos que caracterizan la GCD2: 1) depósitos granulares en en estroma anterior; 2) lesiones tipo *lattice* en el estroma médio-posterior y 3) *haze* estromal anterior. La enfermedad habitualmente empieza con la aparición de depósitos granulares y las lesiones *lattice* son de aparición tardia (cuándo surgen); el *haze* estromal es el signo más tardio de esta distrofia. Es una enfermedad AD relacionada con una mutación conservada del gen *TGFB1*, la mutación p.Arg124His.

Los pacientes con GCD2 pueden presentarse con sensación de cuerpo extraño, dolor y fotofobia secundarios a ECRs. Los pacientes con mutación del gen *TGBF1* en homozigotia tienen início más precoz de la enfermedad y una progresión más rápida de la distrofia, frecuentemente necesitando cirugía en una edad temprana por disminución importante de la agudeza visual.

2.2.2.3. Distrofia corneal lattice tipo 1 (LCD1, OMIM 122200)

La LCD1 es una distrofia AD relacionada con la mutación p.Arg124Cys del gen *TGFB1* en su forma clásica. Sin embargo, existen variantes asociadas con más de 40 mutaciones en 4 de los 17 exones del gen *TGFB1*; el diagnóstico genético de la LCD requiere sequenciación de Sanger de por lo menos esos 4 exones o la sequenciación genómica de *next-generation sequencing*. Se caracteriza por la aparición de líneas de *lattice* finas translucentes durante la primera década de vida en el estromal central anterior, que progresa para la periferia y en profundidad en el estroma corneal y que puede causar *haze* difuso anterior (Figura 4). Los depósitos corneales anteriores resultan en ECRs e irregularidad de la superfície corneal, y el *haze* estromal anterior afecta la agudeza visual. Las líneas de *lattice* tipicamente tienen un contorno doble y un centro claro en retroiluminación, presenteando ramificación dicotómica en sus terminaciones centrales.

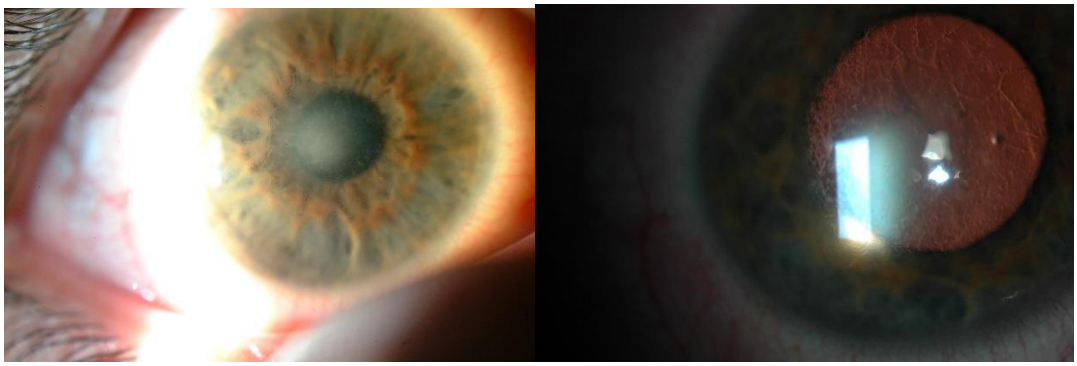


Figura 4 – Distrofia corneal *lattice* tipo 1 (A); la morfologia de los látices se puede apreciar mejor por retroluminación (B).

Histológicamente, los depósitos corneales tiñen de naranja con el rojo Congo y presentan birefringencia bajo luz polarizada. Se observa una desorganización y atrofia epitelial con degeneración de las células epiteliales basales y disrupciones focales de la BL que progresan con la edad. Se observa una capa eosinofílica que separa la MB epitelial de la BL y que es constituída por amilóide y colágeno. Hay una disminución de los números de queratócitos en las áreas afectadas. La membrana de Descemet y endotélio habitualmente son normales.

Se han descrito variantes de la LCD1, incluyendo la variante LCD IIIA (enfermedad AD en que las ECRs son raras y la afectación visual es tardia), la variante III (enfermedad AR con líneas de *lattice* gruesas que se extenden de limbo a limbo), la variante LCD IV (forma atípica de início tardio con depósitos de amilóide profundos en el estroma), así como una forma intermedia entre las LCD1 y la LCD IIIA, conocida como LCD I/IIIA.

3. DISTROFIAS ESTROMALES NO RELACIONADAS CON EL GEN *TGFB1*

3.1. *Distrofia corneal macular (MCD, OMIM 217800)*

La MCD es una distrofia bien definida con una basis genética establecida (categoria 1 de la IC3D). De las 3 distrofias corneales clásicas (GCD1, LCD1, MCD), la MCD es la distrofia menos frecuente pero la que más afecta la visión. Es una enfermedad AR relacionada con el gen *CHST6* (cromosoma 16q22.1) que codifica una sulfotransferasa; la mutación del gen lleva a la pérdida de función de la enzima, llevando a la acumulación de queratano sulfato (KS, del inglés *keratan sulphate*) no sulfatado intra- y extracelular. Histológicamente, se observa 1) el acúmulo de KS no sulfatado entre las lamelas de estroma, que tiñen con azul de Alciano, tinciones metacromáticas y con *periodic acid-Schiff*; 2) se observan frecuentemente guttas en la membrana de Descemet de estos pacientes; 3) degeneración del epitelio corneal en las áreas afectadas; 4) alteraciones de la BL (irregularidad, adelgazamiento o ausencia focal de la BL).

La MCD se puede considerar como un distúrbio localizado de acúmulo de glucosaminoglicanos. Existen diferencias clínicas y patológicas importantes entre la MCD y las mucopolissacaridoses sistémicas (MPS): 1) en las MPS hay manifestaciones extracorneales; 2) en las MPS hay una afectación proeminente del epitélio corneal; 3) en las MPS la Descemet no es afectada; 4) en las MPS el material anómalo se acumula en lisosomas, mientras que en la MCD el material anómalo se acumula en el reticulo endoplasmático.

Clínicamente, la MCD se caracteriza pela aparición de opacidades corneales resultantes de la deposición intra- y extracelular de depósitos de KS en el estroma corneal, que lleva a la pérdida rápidamente progresiva de visión a partir de los 3-9 años de edad; algunos pacientes también pueden tener ECRs si los depósitos se encuentran en el estroma anterior. Inicialmente se observa un *haze* difuso en el estroma central anterior, que se extende progresivamente para la periferia

corneal y para todo el grosor del estroma, con la aparición de opacidades pequeñas, múltiples, pleomorfas y de bordes irregulares sobre todo en el estroma central anterior. En las fases avanzadas, la membrana de Descemet puede tener un aspecto gris y con guttas.

Se han identificado trés inmunotipos clínicos de MCD según la cuantificación de KS en la córnea y en el suero de los pacientes. En la MCD tipo 1, no hay KS sulfatado detectable en el suero ni estroma corneal; en la MCD tipo 1A, no se detecta KS sulfatado en el suero ni en la córnea, pero los queratócitos reaccionan a anticuerpos anti-KS sulfatado; y en la MCD tipo 2, se detecta la presencia de KS sulfatado intra- y extracelular en la córnea, podiendo detectarse también níveles normales o bajos de KS sulfatado en el suero.

3.2. *Distrofia corneal de Schnyder (SCD, OMIM 121800)*

La SCD es una distrofia corneal AD causada por mutaciones en el gen *UBIAD1* (cromosoma 1p36). La proteína SCD-UBIAD1 aberrante es secuestrada en el retículo endoplásmico e inhive la degradación de la enzima HMG-CoA redutasa, que lleva al acúmulo anómalo de lipídios y lipoproteínas en el estroma corneal y a la formación de cuerpos multilamelares, organelos lisosomales intracitoplásmicos conteniendo lipídios.

Clínicamente, la SCD presentase en la segunda o tercera décadas de vida como *haze* corneal central panestromal de forma típicamente discoide. Después de la tercera década de vida, surge el arcus corneal periférico y en estádios más avanzados con la deposición de colesterol en zonas paracentrales (Figura 5). Un 50% de los pacientes tienen depósitos cristalinos subepiteliales. Los pacientes pueden presentar buena visión escotópica pero disfunción visual fotópica devido al *glare* que resulta de la dispersión de luz por el colesterol corneal. Estos pacientes no tienen afectación epitelial ni de la membrana de Descemet y endotélio corneal. La sensibilidad corneal puede disminuir progresivamente en las áreas afectadas, y en microscopia confocal *in vivo* se puede apreciar la pérdida de nervios corneales.

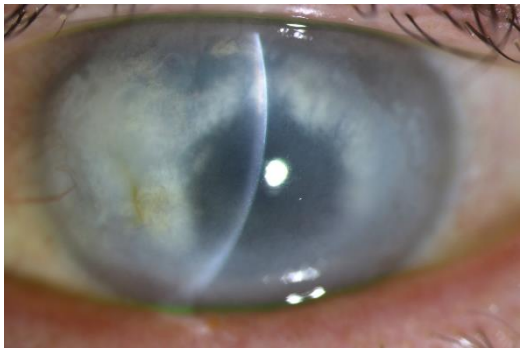


Figura 5 – Distrofia corneal de Schnyder, en un paciente de 64 años de edad con historia de distrofia corneal con más de 40 años de evolución. con opacidad corneal severa panestromal.

3.3. *Otras distrofias corneales estromales*

3.3.1. *Distrofia corneal fleck*

La distrofia corneal *fleck* (FCD, OMIM 121850) es una distrofia corneal con un gen identificado y mutaciones conocidas (categoria 1 de la IC3D) caracterizada por opacidades discretas pequeñas, pleomórficas y grises panestromales de limbo a limbo, no afectando la BL; entre las opacidades, el estroma es normal. Es una enfermedad típicamente bilateral y asimétrica y no progresiva. Los pacientes habitualmente son asintomáticos y la visión es frecuentemente normal. La sensibilidade corneal puede ser afectada. El gen afectado PIKFYVE (cromosoma 2q35) codifica una proteína involucrada en el metabolismo endosomal. Histológicamente, se observan queratócitos edematosos conteniendo vesículas intracitoplasmáticas de mucopolisacarídeos y lipídios.

3.3.2. *Distrofia corneal de François*

La distrofia central de François (CCDF, del inglés *central corneal dystrophy of François*; OMIM 217600) ha sido descrita previamente, pero no hay evidencia clara de que se trate de una entidad clínica distinta (categoria 4 de la IC3D). Es una enfermedad de aparición en la primera década de vida, asintomática y no progresiva, caracterizada por opacidades poligonales grises en el estroma posterior que dan a la córnea el aspecto de "hielo roto". No hay engrosamiento estromal ni alteraciones de la sensibilidad corneal. La ausencia de alteraciones en la periferia y en el estroma anterior son pistas que permiten distinguir entre la CCDF y el *shagreen de cocodrilo* (una degeneración corneal).

3.3.3. Distrofia corneal amorfa posterior

La distrofia corneal amorfa posterior (PACD, OMIM 612868) Es una enfermedad AD resultante de la delección de un *cluster* de genes en el cromosoma 12q21 y que codifican los proteoglicanos queratocano (gen *KERA*), lumicano (gen *LUM*), decorina (gen *DCN*) y epificano (gen *EPYC*), proteiínas involucradas en la fibrillogenesis del colágeno y en la estructuración de la matriz extracelular (categoría 1 de la IC3D). Clínicamente, la PACD es caracterizada por la opacificación del estroma posterior bilateral con disminución del grosor corneal y con aplanamiento de la córnea, con início en la primera década de vida y de carácter lentamente progresivo. Estos pacientes habitualmente presentan alteraciones del íris (corectopia, pseudopolicoria, línea de Schwalbe proeminente y procesos iridianos finos), sin embargo no presentan glaucoma. La PACD es frecuentemente asintomática, pero un 10% de pacientes pueden necesitar queratoplastia por tener opacificación corneal con impacto significativo en la visión.

3.3.4. Distrofia corneal estromal congenita

La distrofia corneal estromal congenita (CSCD, del inglés *congenital stromal corneal dystrophy*; OMIM 610048) es la más rara de las distrofías estromales. Es una enfermedad AD asociada a mutaciones del gen *DCN* (cromosoma 12q21; categoría 1 de la IC3D) que codifica la proteína decorina. Histológicamente, se observan capas de lamelas de colágeno densamente organizadas (con patrón similar a las lamelas corneales normales) alternando con capas de fibrillas de colágeno desordenadas. El endotélio corneal es normal y la membrana de Descemet es de grosor normal, a pesar de que presenta una capa bandeada anterior menos desarrollada de lo normal. Clínicamente, se caracteriza por opacificación corneal congenita bilateral no progresiva (o lentamente progresiva), con *haze* estromal difuso y opacidades estromales focales blancas en el estroma central anterior. El epitélio corneal es normal, no hay alteraciones de la sensibilidad corneal, y la paquimetria corneal es normal. Es una enfermedad ambliogenica y que puede causar nistagmus.

3.3.5. Distrofia predescemética

La distrofía predescemética (PDCD, del inglés *pre-Descemet corneal dystrophy*) puede ocurrir como enfermedad aislada (categoría 4 de la IC3D) o asociada a la ictiosis relacionada con el cromosoma X recesiva (cromosoma Xp22.3 gen *STS* que codifica la proteína sultafasa de esteroides; distrofia de categoria 1 de la IC3D). Se caracteriza por la presencia de opacidades discretas grises lineares o punteadas en el estroma posterior predescemético y que pueden se difusas, centrales o anulares. Es una enfermedad habitualmente bilateral y simétrica que se presenta después de los 30 años de edad y que habitualmente no afecta la visión.

4. DISTROFIAS ENDOTELIALES

4.1. Distrofia endotelial de Fuchs

La distrofia endotelial de Fuchs (FECD, del inglés *Fuchs' endothelial corneal dystrophy*) es la segunda distrofia corneal más común, después de la EMBD. Es una enfermedad del endotélio corneal bilateral, caracterizada por la pérdida acelerada de células endoteliales con alteraciones patológicas de la membrana de Descemet, incluyendo el acúmulo de matriz extracelular y la formación de guttas corneales. Es una enfermedad que afecta primariamente el endotélio corneal y membrana de Descemet, pero que con la progresión de la enfermedad lleva a alteraciones secundárias de todas las capas de la córnea así como de los nervios corneales (con disminución del número de nervios corneales y de troncos corneales principales). Histológicamente, se observan: 1) la pérdida accelerada y progresiva de las células endoteliales con alteraciones progresivas de las células remanentes (disfunción metabólica y oxidativa, aumento de tamaño celular – polimegatismo – y cambios de forma celular – pleomorfismo); 2) adelgazamiento o ausencia de la capa posterior no bandeada de la membrana de Descemet, la aparición de una capa

fibrosa (“border layer”) y de una capa de células endoteliales pleomórficas al nível de la Descemet – “Capa fibrillar”); 3) a nível estromal, activación de queratócitos estromales y fibrosis subepitelial en los estadios avanzados de la distrofia; 4) alteraciones epiteliales, con edema intracelular de las células basales y edema intercelular de las capas epiteliales superficiales con aparición de bullas epiteliales en la enfermedad avanzada.

Se han identificado dos formas de FECD. La FECD de início precoz (FECD1, categoría 1 de la IC3D) es una enfermedad rara de herencia AD y aparición de alteraciones clínicas en la primera década de vida, y que está relacionada con el gen *COLA82* (cromosoma 1p34.3-p32) que codifica da cadena alfa-2 del colágeno tipo VIII, un importante componente de la membrana de Descemet. La FECD de início tardio es claramente la variante más frecuente, con una prevalencia global estimada de un 7.33% (intervalo de confianza de 95%: 4.08-12.8%) según una revisión sistemática y meta-análisis reciente por Aiello y colaboradores. (Aiello et al. J Ophthalmol, 2022) La FECD de início tardio es de categoría 3 de la IC3D, ya que no se identifica un *locus* genético en la mayoría de los pacientes; sin embargo, algos pacientes presentan mutaciones en algunos *loci*, incluyendo los genes *SLC4A11, ZEB1, LOXHD1* y *AGBLI* (categoría 2 de la IC3D). Esta distrofía es probablemente de etiología multifactorial; sin embargo, la expansión de trinucleotídeos repetidos del gen *TCF4* (cromosoma 18q); esta alteracion genética es posiblemente asociada a la FECD tardia en la mayoria de los pacientes caucasianos (variante FECD3).

La FECD de início tardio suele presentarse clínicamente en la quinta década de vida, con una prevalencia 2.2 veces superior en mujeres. En los estádios iniciales de la enfermedad, puede ser asintomática. Las limitaciones subjetivas en las actividades diarias relacionadas con la FECD incluyen la disminución de la visión, el *glare*, la fluctuación diurna de la visión (el empeoramiento de la visión por la mañana es un síntoma sugestivo de disfunción endotelial) y dolor ocular. La progresión de la enfermedad es evidente clínicamente, con la aparición de guttas corneales, pérdida endotelial accelerada y descompensación corneal con aparición de edema estromal, queratopatía bullosa y eventualmente enfermedad terminal con fibrosis subepitelial y cicatrización estromal. El diagnóstico es clínico y auxiliado por métodos de diagnóstico que también permiten monitorar la progresión de la distrofia, como la microscopia especular, la tomografia corneal, la OCT de segmento anterior y la paquimetría.

Existen multiples clasificaciones clínicas de la FECD. La primera clasificación por Krachmer es basada en el número y localización de las guttas corneales, así como la presencia de edema corneal:

- Grado 1: 0 ≤12 guttas centrales
- Grado 1: 1 >12 guttas centrales no confluentes
- Grado 2: 1–2 mm guttas centrales confluentes
- Grado 3: 2–5 mm guttas centrales confluentes
- Grado 4: >5 mm guttas centrales confluentes
- Grado 4 con edema : >5 mm guttas centrales confluentes y edema estromal y/o epitelial

Tradicionalmente se ha utilizado una clasificación clínica de 4 estádios (Mannis MJ and Holland EJ. Cornea – Fundamentals, Diagnosis and Management (Chapters 69-72). Fifth Edition. Elsevier (2022)).

- Estádio 1: guttas corneales centrales central corneal guttae
- Estádio 2: extension periférica de las guttas corneales y coalescencia de guttas con aspect de metal batido; puede tener pigmento endotelial ("dusting"), engrosamiento y/o estrias en la membrana de Descemet; y evoluciona para descompensación endotelial con edema estromal
- Estádio 3: queratopatía bullosa
- Estádio 4: enfermedad terminal "end-stage", con fibrosis subepitelial y cicatrización anterior avascular entre el epitélio y la capa de Bowman

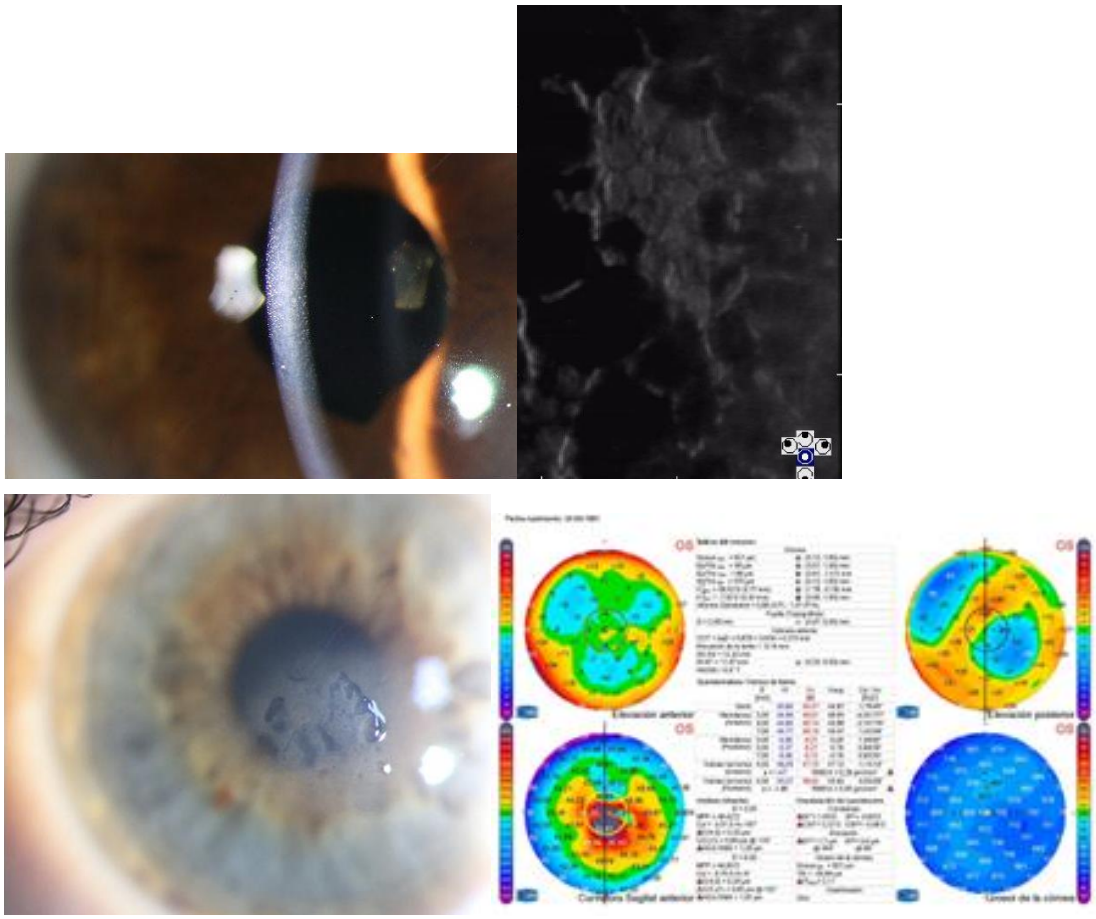


Figura 6 – Distrofia corneal endotelial de Fuchs de início tardio. Un caso de distrofía con guttas difusas y densas (A) y un caso de distrofía avanzada (C), donde se observan bullas epiteliales, edema stromal significativo y engrosamiento de la membrana de Descemet. En topografía corneal de este caso avanzado (D), se observa engrosamiento corneal con isopacas irregulares en el mapa paquimétrico, depression de la superfície posterior en el mapa de elevación posterior, y alteraciones queratométricas en el mapa de curvatura sagital. En microscopía especular, se observa disrupción del mosaico endotelial, guttas, disminución del contaje de células endoteliales, pleomorfismo) y polimegatismo (B).

4.2. Distrofia corneal polimorfa posterior

La distrofia corneal polimorfa posterior (PPCD, del inglés *posterior polymorphous corneal dystrophy*) es una enfermedad heterogenea del punto de vista genético, identificandose 4 entidades distintas: la PPCD1 (*locus* 20p11.2-q11.2, sin gen identificado), la PPCD2 (gen *COL8A2*, *locus* 1p34.3-p32.3), la PPCD3 (gen *TCF8*, *locus* 10p11.2; y algunos casos el gen *ZEB1*) y la PPCD4 (gen *GRLH2*, *locus* 8q22.3-q24.12).

Clínicamente, la PPCD se presenta en edad infantil con la presencia de lesiones vesiculares, lesiones en banda y/o opacidades difusas bilaterales (pero que pueden ser asimétricas). En la

mayor parte de los casos, es estable y asintomática. La lesión vesicular al nível de la membrana de Descemet es la lesión clásica de esta distrofia; en la microscopia especular, son excavaciones de la Descemet posterior que se observan como manchas negras que interrumpen el mosaico endotelial. Las lesiones en banda son típicamente horizontales y habitualmente de localización paracentral inferior; en la microscopia especular, se observan células endoteliales aumentadas y pleomórficas delineando las bandas. Es infrecuente la aparición de edema corneal, pero puede cursar con queratopatia bullosa. Un cuarto de los pacientes tienen sinéquias anteriores periféricas, y un 15% de los pacientes pueden presentar presión intraocular elevada. Algunos pacientes con PPCD pueden presentar aumentos significativos de la curvatura corneal o signos de ectasia corneal.

El principal diagnóstico diferencial de la PPCD es con los síndromes iridocorneoendoteliales (ICE), ya que ambas enfermedades pueden presentar sinéquias anteriores periféricas, alteraciones iridianas, presión intraocular aumentada y edema corneal. La PPCD es típicamente bilateral y hereditária, mientras que los síndromes ICE son esporádicos y unilaterales, y en la microscopia especular las células en los síndromes ICE son negras con un punto central blanco ("células ICE").

4.3. Distrofia endotelial congenita hereditária (OMIM 217700)

La distrofia endotelial congenita hereditária (CHED, del inglés *congenital hereditary endothelial dystrophy*) fue descrita por primera vez en 1893 como *"corneitis interstiliasis in utero*". Antes de 2015, se consideraban una forma AD (CHED1) y una forma AR (CHED2), pero tras la revisión de la clasificación de la IC3D la CHED1 se considera como siendo casos de PPCD y la CHED se reporta exclusivamente a la forma autosómica reesiva. Es una enfermedad asociada a mutaciones del gen *SLC4A11* (*locus* 20p13-12) que codifica un cotransportador de sódio-borato en la membrana celular (categoria 1 de la IC3D); la pérdida de función de este cotransportador lleva a la pérdida del control de la regulación y diferenciación de las células del endotélio corneal, con muerte celular y edema corneal progresivo. Algunos pacientes pueden presentar sordez perceptiva asociada al CHED – síndrome de Harboyan.

La CHED se presenta con edema corneal congenito severo, bilateral pero frecuentemente asimétrico; la opacificación corneal se extende hasta el limbo. Hay un aumento significativo del grosor corneal; el epitélio tiene un aspecto irregular o arrugado; y habitualmente la membrana de Descemet no se visualiza pero está engrosada.

Patológicamente, la CHED presenta los siguientes hallazgos: 1) alteraciones epiteliales secundarias el edema corneal crónico; 2) pérdida variable de la capa de Bowman; 3) engrosamiento estromal muy marcado con disrupción y desorganización de las lamelas corneales; 4) engrosamiento de la membrana de Descemet, con una zona no bandeada posterior anómala

pero con zona bandeada anterior normal; 5) Ausencia o degeneración marcada de las células endoteliales.

4.4. Distrofia endotelial asociada al cromosoma X (XECD, OMIM 300779)

Se ha descrito una única família con una distrofia endotelial relacionada con el cromosoma X, mapeada al *locus* Xq25 pero sin identificación del gen mutado (categoria 2 de la IC3D). Se caracteriza por edema corneal congenito más grave en el sexo masculino; algunos pacientes presentan queratopatia en banda secundaria. En el sexo feminino, se observan alteraciones asintomáticas del endotélio corneal similares a crateras lunares.

5. DIAGNÓSTICO POR IMAGEN DE LAS DISTROFIAS CORNEALES

El diagnóstico diferencial de las distrofias corneales es frecuentemente un reto clínico. Las modalidades de diagnóstico por imagen han permitido identificar aspectos clínicos que permiten distinguir distrofias de otras enfermedades y las distrofias entre ellas.

5.1. Microscopia confocal *in vivo* (IVCM)

La IVCM es una técnica no invasiva que permite examinar las células corneales, las fibras de colágeno y morfología de los nervios corneales y pernite valorar la córnea capa por capa y valorar la profundidad de lesiones corneales con elevada resolución. Permite apoyar en el diagnóstico, determinar progresión y entender la fisiopatología de las distrofias corneales, siendo particularmente útil en casos donde el diagnóstico no es evidente por biomicroscopía por lámpara de hendidura y en la investigación científica de estas enfermedades raras. Las alteraciones microestructurales identificadas en las distrofias a traves de la IVCM se relacionan fuertemente con la histopatología y con la presentación clínica. Se recomienda el artículo de Shukla y colaboradores (Shukla et al. Semin Ophthalmol, 2012) para una revisión extensa de las alteraciones particulares de cada distrofia corneal en IVCM.

5.2. Microscopia especular

La microscopia especular permite valorar la presencia de guttas y el mosaico endotelial en pacientes con distrofias estromales posteriores y en pacientes con distrofias endoteliales. En la PPCD, se observan las vesículas clásicas como manchas negras que interrumpen el mosaico endotelial, y también se observan las lesiones en banda como anteriormente descrito. En la FECD se observan las guttas corneales, la pérdida progresiva de células endoteliales y el cambio

morfológico del mosaico endotelial con alteración de la forma y dimensión de las células endoteliales remanentes (pleomorfismo y polimegatismo).

5.3. Tomografia de coherencia óptica de segmento anterior (OCT-SA)

La OCT-SA permite la valoración de cada capa de la córnea con elevada resolució, casí con resolución histológica. Con la OCT-SA se puede determinar la profundidad, dimensión, morfología y extensión de múltiples distrofias corneales. En casos de edema o opacidad corneal marcada, la OCT-SA permite además valorar detalles y estructuras que de otro modo no serían apreciables por biomicroscopía con lámpara de hendidura (Siebelmann et al. Surv Ophthalmol, 2018).

Algunos ejemplos relevantes incluyen: 1) la EMBD, donde se observan irregulareidades de la MB epitelial con protrusiones que invaden el epitélio corneal; 2) las distrofias de la BL, donde se observan depósitovs hiperreflectivos al nível de la capa de Bowman y el aspecto en sierra dentada de la TBCD permite la distincción de la RBCD; 3) en la LCD, las líneas de *lattice* corresponden a depósitos hiperreflectivos en el estroma anterior y médio, con áreas de interrupción de la BL; 4) en las distrofias granulares (GCD1 y GCD2) las opacidades corneales se presentan como depósitos hiperreflectivos en la OCT-SA y provocan efecto de sombra para el estroma subyacente; 5) en la FECD, se observa un engrosamiento de la membrana de Descemet y zonas aisladas de engrosamiento nodular del endotélio corneal. En estadios con edema corneal, se observa el engrosamiento estromal y las alteraciones epiteliales del edema corneal crónico, incluyendo fibrosis subepitelial.

Se recomienda el capítulo de Libro *"Optical Coherence Tomography in Corneal Dystrophies* de Siebelmann, Güell y colaboradores (doi: 10.1007/978-3-031-07730-2_8) para una revisión extensa de las alteraciones particulares de cada distrofia corneal por OCT-SA.

6. DIAGNÓSTICO DIFERENCIAL DE LAS DISTROFIAS CORNEALES

Las distrofias corneales son enfermedades raras, habitualmente hereditárias y de presentación bilateral. Los principales diagnósticos diferenciales de las diferentes distrofias corneales están relacionados con los síntomas y con el aspecto morfológico. Algunas distrofias corneales pueden confundirse con enfermedades degenerativas corneales, que también son típicamente bilaterales. En un paciente con ECRs, es importante excluir las distrofias epiteliales, las distrofias de la BL y algunas distrofias estromales. La presencia de *lattices* en el estroma corneal que caracterizan las distrofias LCD y GCD2 justifica la investigación de una posible enfermedad amilóide sistémica. En pacientes con hallazgos corneales sugestivos de MCD o de SCD, es importante excluir enfermedades metabólicas sistémicas (como la hiperlipidemia en la SCD).

La FECD es la causa más común de córnea guttata. Sin embargo, algunos sujetos sin patología pueden presentar guttas en la periferia corneal (cuerpos de Hassall-Henle), y el diagnóstico diferencial de guttas debe incluir los síndromes ICE (tipicamente unilateral, con alteraciones corneales, iridianas, sinéquias anteriores periféricas y glaucoma), las endoteliitis víricas por vírus de la família *Herpesviridae*, la queratitis intersticial, los síndromes ICE y otras distrofias corneales como la MCD y la PPCD. Además, algunos ojos con historia de traumatismo o de inflamación intraocular pueden presentar pseudoguttas corneales.

Finalmente, las distrofias estromales posteriores congenitas y las distrofias endoteliales congenitas integran el cuadro de diagnósticos diferenciales de edema corneal congenito – glaucoma congenito, enfermedades metabólicas, anomalia de Peters, infecciones congenitas, traumatismo con forceps.

7. TRATAMIENTOS PARA PACIENTES CON DISTROFIAS CORNEALES

El tratamiento de las distrofias corneales está indicado en casos sintomáticos y/o con afectación de la función visual. Las modalidades terapéuticas son distintas según el tipo de distrofia, y se pueden agrupar como tratamientos de ECRs sintomáticas y tratamientos para rehabilitación visual. Para el tratamiento de ECRs, se pueden considerar los tratamientos conservadores no invasivos (lubricación ocular, colírios o unguentos de solución salina hipertónica al 5%) y tratamientos invasivos como la micropunción estromal anterior, la queratectomía superficial (mecánica o con alcohol) y la queratectomía fototerapéutica (PTK) con láser de excimer. Para rehabilitación visual, actualmente se pueden considerar la PTK y la queratoplastía.

7.1. Queratectomía fototerapéutica (PTK)

La PTK con láser de excimer es una técnica rápida, poco invasiva, segura y eficaz para el tratamiento de opacidades corneales afectando el tercio anterior de la córnea en pacientes con distrofias corneales causando ECRs y/o disminución de la agudeza visual – distrofias epiteliales (EMBD, GDLD), distrofias de la BL (RBCD, TBCD), distrofias estromales relacionadas con el gen *TGFB1*, distrofia macular y distrofia de Schnyder (Ashena et al. Vision, 2023). Un 90% de los pacientes con distrofias corneales sintomáticas (ECRs y disminución de agudeza visual) mantienen o mejoran la agudeza visual corregida y dejan de tener sintomas de ECRs; pero una tasa relativamente alta de pacientes tienen recurrencias de la distrofia (entre 20-40% de los casos) (Figura 7) (Stewart et al. Eye, 2002) (Figura 6). En los casos de ablaciones más profundas (por ejemplo más de 50 micras de estroma) se puede observar un cambio refractivo hipermetrópico y que puede ser manejado mediante un plano de ablación anti-hipermetrópico concomitante. Para minimizar el riesgo de *haze* post-PTK y para disminuir el riesgo o retrasar la recurrencia de

opacidades corneales tras el tratamiento, algunos cirujanos defenden la utilización de mitomicina C durante el tratamiento con PTK.

Además, la PTK es efectiva para tratar opacidades de distrofias corneales que aparecen postoperatoriamente (recurrentes), tanto post-PTK como post-queratoplastia, y por lo tanto es una técnica que puede ser adoptada para pacientes con recurrencias frecuentes de sus opacidades (Zeng et al. BMC Ophthalmol, 2019).

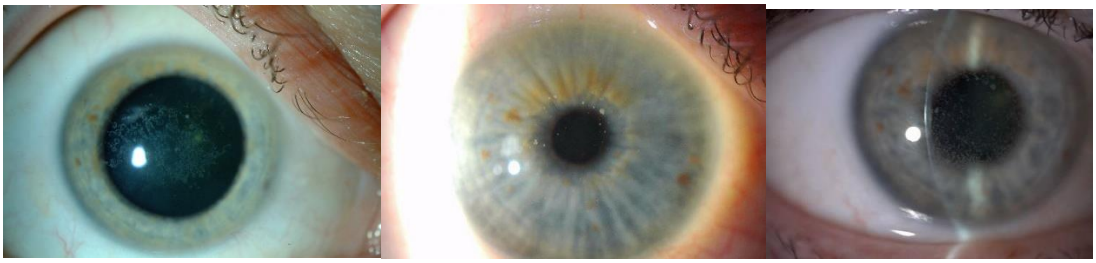


Figura 7 – Recurrencia de distrofia corneal estromal tras queratectomía fototerapéutica con láser de excímeros – pre-tratamiento (A), post-tratamiento (B) y recurrencia (C).

7.2. Queratoplastia

En pacientes con distrofias corneales causando opacificación, *haze* corneal o edema corneal franco, puede estar indicada la realización de queratoplastía penetrante (QPP) o lamelar para mejorar la agudeza visual. En las distrofías anteriores con opacidades o fibrosis anterior, se puede valorar la queratoplastía lamelar anterior profunda (DALK) como técnica de elección, atendiendo a las ventajas de esta técnica en comparación con la QPP (evitar cirugía "a cielo abierto", menor riesgo de rechazo inmunológico y preservación del endotélio corneal) (Figura 8). (Unai et al. Cornea, 2013) En las distrofias endoteliales con afectación visual importante, está ampliamente demostrada la elevada efectividad y seguridad de las técnicas de queratoplastía endotelial (DSAEK y DMEK) (Figura 9) y su mejor perfil en comparación con la QPP en estos ojos (recuperación visual más rápida, predictibilidad refractiva, menor riesgo de rechazo inmunológico y menor pérdida de células endoteliales a largo plazo). Sin embargo, la QPP puede estar indicada en algunos pacientes con distrofias endoteliales, particularmente en los casos de FECD con edema estromal crónico y con fibrosis subepitelial o estromal anterior importante.

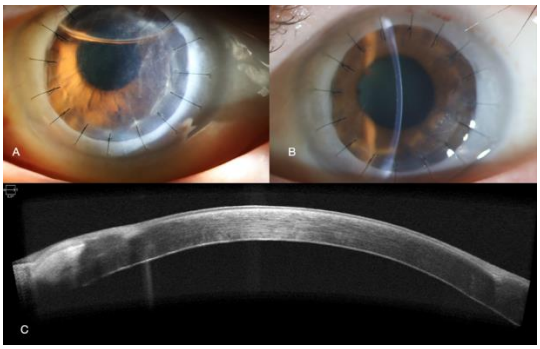


Figura 8 – Queratoplastía lamelar anterior profunda (DALK) en un paciente con distrofía corneal de Schnyder. Fotografias de segmento anterior, donde se aprecia burbuja de gas por presentar doble cámara anterior en el postoperatorio precoz (A) y tras resolución del cuadro (B); en la OCT de segmento anterior se aprecia en injerto DALK con correcta aposición (C).

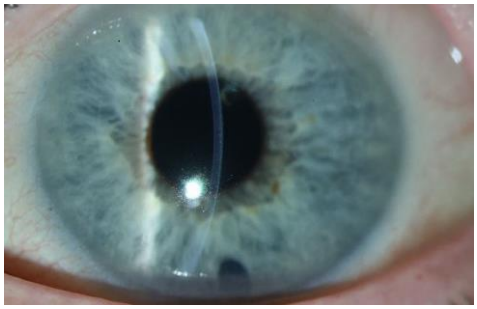


Figura 9 – Queratoplastía endotelial de membrana de Descemet (DMEK) en un paciente con distrofía del endotélio corneeal de Fuchs.

Las distrofias de la BL y las distrofias estromales relacionadas con el gen *TGFB1*, la MCD y la SCD se asocian a un riesgo elevado de recurrencias en los injertos de queratoplastia. En los pacientes con CSCD, la QPP está indicada precozmente para prevenir la ambliopia irreversible; notablemente, no se han observado casos de recurrencias de opacidades estromales en estos pacientes. De la misma manera, los pacientes con opacidad o edema corneal congenito relacionado con distrofias corneales pueden necesitar queratoplastia en edades muy precoces, y los injertos corneales tradicionalmente se asocian a un peor pronóstico en estos grupos de pacientes.

En algunos pacientes seleccionados con FECD centrales y endotélio periférico sano, la Descemetorrhexis sin queratoplastía endotelial (DSO o DWEK) y el trasplante de membrana de Descemet han surgido con estratégias potencialmente interesantes (Franchescino et al. Cornea, 2022),. Sin embargo, todavía no disponemos de datos de resultados a largo plazo de estas técnicas, al contrário de la DMEK y DSAEK; y todavía no hay evidencia definitiva de si la suplementación con inhibidores de la Rho kinasa (RKIs) mejora los resultados de la DSO en estos casos (Moloney et al. Cornea, 2017; Moura-Coelho et al. Graefes Arch Clin Exp Ophthalmol, 2019).

7.3. Perspectivas futuras en el tratamiento de las distrofias corneales

La comprensión creciente de la fisiopatología y genética de las distrofias corneales hace que estas enfermedades sean le gran interés para la medicina regenerativa, "customizada" y las terapías genéticas que han conocido avances importantes en la última década. Algunos estudios con pocos pacientes sugeren que la inyección intracameral de células endoteliales humanas cultivadas *in vitro* suplementada con RKIs mejora la agudeza visual en pacientes con edema bulloso (Kinoshita et al. NEJM, 2018; Numa et al. Ophthalmology, 2021).

La terapía genica con oligonucleotídeos "*anti-sense"* (ARN de interferencia) y con técnicas de edición genética (*CRISPR/Cas9*) son alternativas interesantes en las distrofías corneales con mutaciones genéticas identificadas, por ejemplo para las distrofías relacionadas con el gen *TGFB1* y en los pacientes con FECD y con expansión de trinucleotídeos CTG del *locus TCF4*. (Han et al. Prog Retin Eye Res, 2016; (Spiteri et al.Vision, 2021).

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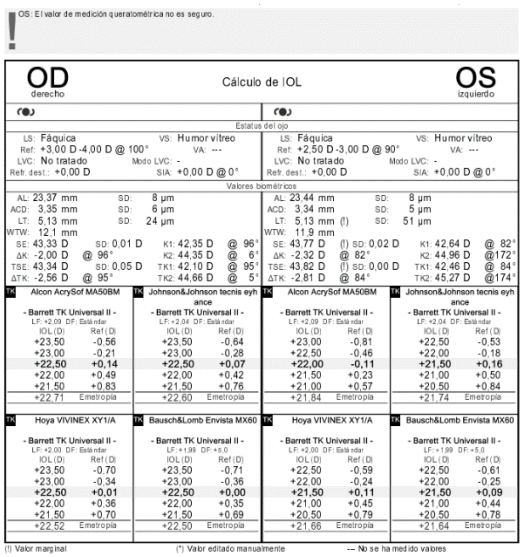
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Caso Clínico 1

Paciente referido por visión borrosa y sensación de cuerpo extraño tras cirugía de catarata en ambos ojos 9 meses antes. Aportaba la siguiente información clínica preoperatoria:

- AV OD +3,00 -4,00 (100º) = 0,8
- AV OI +2,50 -3,00 (90º) = 0,6+
- LH: Blefaritis anterior, epitelio irregular y catarata corticonuclear en AO.
- Biometria (fig. 1) - LIO implantada en OD monofocal tórica, en OI monofocal no tórica.



OS: El valor de medición queratométrica no es seguro.

OD derecho	Cálculo de IOL	OS izquierdo

Estatus del ojo

OD	OS
LS: Fáquica — VS: Humor vítreo Ref: +3,00 D -4,00 D @ 100° — VA: --- LVC: No tratado — Modo LVC: - Refr. dest.: +0,00 D — SIA: +0,00 D @ 0°	LS: Fáquica — VS: Humor vítreo Ref: +2,50 D -3,00 D @ 90° — VA: --- LVC: No tratado — Modo LVC: - Refr. dest.: +0,00 D — SIA: +0,00 D @ 0°

Valores biométricos

OD	OS
AL: 23,37 mm — SD: 8 µm ACD: 3,35 mm — SD: 6 µm LT: 5,13 mm — SD: 24 µm WTW: 12,1 mm SE: 43,33 D — SD: 0,01 D — K1: 42,35 D @ 96° ΔK: -2,00 D @ 96° — K2: 44,35 D @ 6° TSE: 43,34 D — SD: 0,05 D — TK1: 42,10 D @ 95° ΔTK: -2,56 D @ 95° — TK2: 44,66 D @ 5°	AL: 23,44 mm — SD: 8 µm ACD: 3,34 mm — SD: 5 µm LT: 5,13 mm (!) — SD: 51 µm WTW: 11,9 mm SE: 43,77 D (!) — SD: 0,02 D — K1: 42,64 D @ 82° ΔK: -2,32 D @ 82° — K2: 44,96 D @172° TSE: 43,82 D (!) — SD: 0,00 D — TK1: 42,46 D @ 84° ΔTK: -2,81 D @ 84° — TK2: 45,27 D @174°

TK Alcon AcrySof MA50BM — Barrett TK Universal II		TK Johnson&Johnson tecnis eyhance — Barrett TK Universal II	
IOL (D)	Ref (D)	IOL (D)	Ref (D)
+23,50	-0,56	+23,50	-0,64
+23,00	-0,21	+23,00	-0,28
+22,50	**+0,14**	**+22,50**	**+0,07**
+22,00	+0,49	+22,00	+0,42
+21,50	+0,83	+21,50	+0,76
+22,71	Emetropía	+22,60	Emetropía

TK Alcon AcrySof MA50BM — Barrett TK Universal II		TK Johnson&Johnson tecnis eyhance — Barrett TK Universal II	
IOL (D)	Ref (D)	IOL (D)	Ref (D)
+23,00	-0,81	+22,50	-0,53
+22,50	-0,46	+22,00	-0,18
+22,00	**-0,11**	**+21,50**	**+0,16**
+21,50	+0,23	+21,00	+0,50
+21,00	+0,57	+20,50	+0,84
+21,84	Emetropía	+21,74	Emetropía

TK Hoya VIVINEX XY1/A — Barrett TK Universal II		TK Bausch&Lomb Envista MX60 — Barrett TK Universal II	
IOL (D)	Ref (D)	IOL (D)	Ref (D)
+23,50	-0,70	+23,50	-0,71
+23,00	-0,34	+23,00	-0,36
+22,50	**+0,01**	**+22,50**	**+0,00**
+22,00	+0,36	+22,00	+0,35
+21,50	+0,70	+21,50	+0,69
+22,52	Emetropía	+22,50	Emetropía

TK Hoya VIVINEX XY1/A — Barrett TK Universal II		TK Bausch&Lomb Envista MX60 — Barrett TK Universal II	
IOL (D)	Ref (D)	IOL (D)	Ref (D)
+22,50	-0,59	+22,50	-0,61
+22,00	-0,24	+22,00	-0,25
+21,50	**+0,11**	**+21,50**	**+0,09**
+21,00	+0,45	+21,00	+0,44
+20,50	+0,79	+20,50	+0,78
+21,66	Emetropía	+21,64	Emetropía

(!) Valor marginal — (*) Valor editado manualmente — --- No se ha medido valores

Figura 1. Biometria óptica de paciente.

- Topografia corneal preoperatoria (fig. 2)

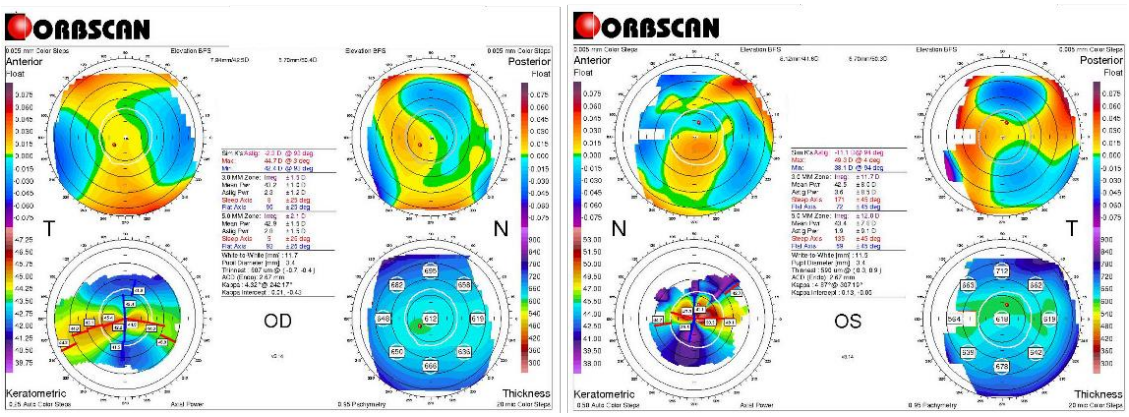


Figura 2: Topografía corneal de paciente antes de su cirugía de catarata.

A la exploración oftalmológica a presentación en nuestro centro, la agudeza visual era de:

AV OD +1,00 -0,50 (40º) = 1,0—

AV OI +2,75 -3,00 (85º) = 0,8-

Con refracción el paciente comenta borrosidad en AO constante y subjetivamente “quizas peor tras la cirugía de catarata”.

LH: Ausencia de signos de blefaritis. Alteraciones epiteliales tipo huella en AO más evidentes en OI. Pseudofaquia en saco capsular en AO.

Se realizó topografía corneal (fig. 3).

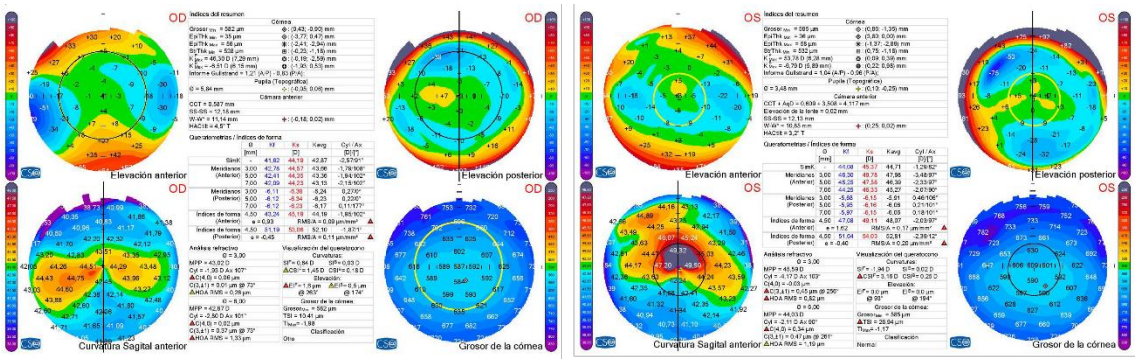


Figura 3: Tomografía corneal de paciente a la presentación en nuestro centro.

Se optó por realizar queratectomía superficial con desbridamiento epitelial. A los 7 meses de seguimiento, este era el resultado:

- AV OD +0,75 -0,25 (175º) = 1,0
- AV OI +1,00 -1,00 (80º) = 1,0

Sin borrosidad en AO y menor dependencia de gafas, epitelio regular y cornea transparente en AO.

Se realizó topografía corneal (fig. 4).

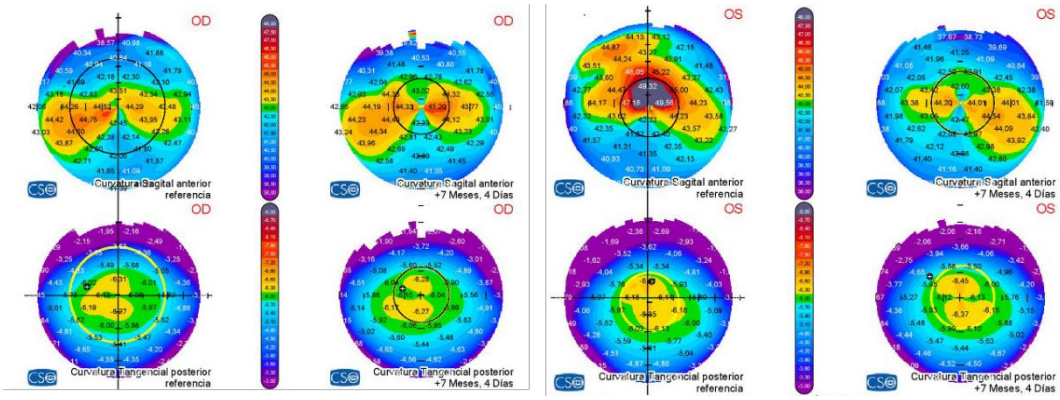


Figura 4: Tomografía corneal de paciente tras el tratamiento.

1- Con respecto al caso clínico 1, elija la opción *verdadera*:

a) La prevalencia estimada de esta distrofia corneal es de un 3% de la población

b) Los hallazgos descritos en lámpara de hendidura a la presentación en nuestro centro corresponden a la acumulación de sustancia peculiar en las células epiteliales en microscopía electrónica de transmisión

c) En estos casos, está contraindicado realizarse desbridamiento epitelial antes de la cirugía de catarata, una vez que no influye la predictibilidad refractiva de la cirugía de catarata

d) Esta distrofia corneal en algunos casos está asociada a mutaciones del gen *TCF4*, y en estos casos se considera una distrofia de categoría 1 de la IC3D

e) Ninguna de las afirmaciones anteriores es correcta.

2. Respecto al caso clínico 1, sobre el tratamiento de esta situación clínica, ¿cuál de las siguientes afirmaciones es *correcta?*

a) La queratectomía fototerapéutica con láser de excímer está contraindicada en esta distrofia

b) Los colírios y ungüentos de solución salina hipotónica al 0,05% son el tratamiento conservador de elección en pacientes con erosiones corneales recurrentes asociados a esta enfermedad corneal

c) Los tratamientos invasivos para tratamiento de erosiones corneales recurrentes en pacientes con esta distrofia son definitivos, no se observando recurrencias de esta distrofia tras el tratamiento

d) En este paciente, podría plantearse cirugía refractiva corneal láser si el paciente desea independencia de gafas.

e) La terapía genica con la técnica de edición genética *CRISPR* del gen *TCF4* está indicada en pacientes con esta distrofia corneal.

Caso Clínico 2

Varón 68 años_historia de enfermedad corneal bilateral y con empeoramiento progresivo de AV sobre todo en OI (fig. 1). A la presentación en nuestro centro, se observó:

AV +4,00 -2,25 (45º) = 0,6-

AV +4,50 -3,50 (130º) = 0,3-

Ojo derecho Ojo izquierdo

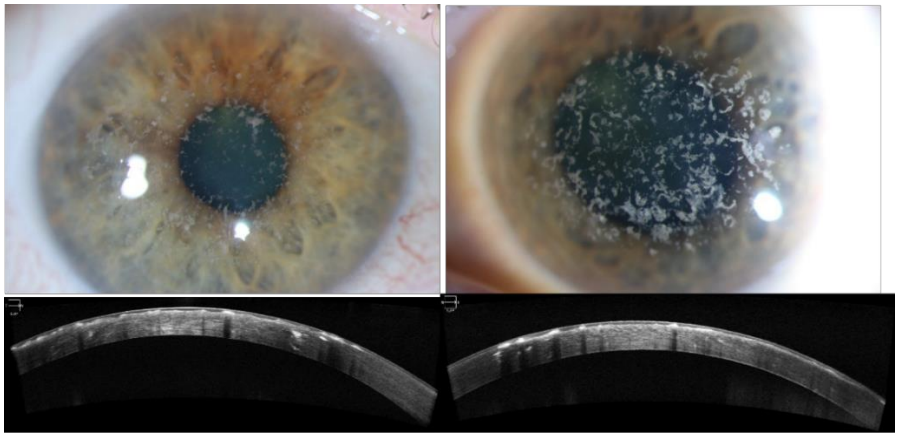


Figura 1. Fotografía de segmento anterior y OCT de segmento anterior.

3. Sobre la situación clínica descrita en el caso clínico 2, elija la opción *correcta:*

a) La histología de esta distrofia típicamente consiste en depósitos estromales que tiñen con azul de Alciano y fuertemente con *periodic acid-Schiff*

b) En esta distrofia, ocurre la sustitición de la capa de Bowman por una capa fibrocelular

c) En esta distrofia, es frecuente observarse guttas en la membrana de Descemet

d) La afectación visual habitualmente ocurre a partir de la quinta década de vida por coalescencia de las opacidades o por la opacificación del estroma adyacente a estas opacidades.

e) En esta distrofia corneal es típica la presencia de depósitos cristalinos subepiteliales, que se observan en un 50% de los casos

4. Sobre la situación clínica descrita en el caso clínico 2, elija la opción *correcta:*

a) Esta distrofia es la distrofia estromal más prevalente en países Occidentales

b) En esta distrofia, se puede observar el acúmulo de queratano sulfato no sulfatado entre las lamelas del estroma corneal

c) Esta distrofia está asociada a alteraciones de la sensibilidad corneal.

d) El diagnóstico genético de esta distrofia implica la secuenciación de múltiples exones o *next-generation sequencing*.

e) La presentación inicial de esta distrofia consiste en opacidades corneales de distribución panestromal central, progresando hacia la periferia

5. En el caso clínico 2, tras el tratamiento con PTK transepitelial en su ojo izquierdo, la AV mejoró a +4,00 -2,25 (120º) = 0,7+, estable a los 3 años de seguimiento. En OD la AV se mantuvo estable, sin nuevas lesiones. ¿Cuál de las siguientes afirmaciones considera *incorrecta*?

a) La PTK con láser de excímeros puede ser combinada con ablación antihipermetrópica en ojos con opacidades estromales de profundidad de 100 micras

b) La probabilidad de recurrencias de opacidades corneales tras la PTK con láser de excímeros se sitúa entre un 20 y un 40%

c) La PTK está contraindicada en ojos con recurrencias de esta distrofia corneal en ojos operados de queratoplastia

d) La PTK puede ser repetida en casos de opacidades corneales recurrentes, con buenos resultados a largo plazo demostrados en estos retratamientos

e) Esta distrofia corneal es una potencial candidata a las terapias génicas en desarrollo actualmente.

Reference (List of Scientific Publications): XIX: Moura-Coelho, N., & Güell, J.L. (2021c) *Queratoplastia laminar endotelial In: Cirugia corneal y refractiva – Libro de residentes de la Sociedad Española de Oftalmología*.

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2.4. Queratoplastia Laminar Endotelial

La queratoplastía laminar endotelial (EK, del inglés *Endothelial Keratoplasty*) consiste en la remoción del complejo endotelio corneal y membrana de Descemet (EDM, del inglés *Endothelium-Descemet Membrane*) del receptor, con inserción de un injerto laminar posterior de un donante, el cual es aplicado contra el estroma de la córnea receptora con una burbuja de gas. [1] Descrita por primera vez en 1956 (Tillett), fue a partir de 1998 que la EK tuvo un desarrollo importante, cuando Melles describió la técnica de queratoplastía laminar endotelial profunda (DLEK, del inglés *Deep Lamellar Endothelial Keratoplasty*). Sin embargo, esta técnica era técnicamente compleja porque requería la disección manual del receptor y del donante y, en 2004, Melles modificó su técnica al incluir la remoción del complejo EDM del estroma posterior del receptor (descemetorhexis) con trasplante de endotelio, Descemet y estroma posterior del donante, designada DSEK por Price (del inglés *Descemet Stripping Automated Keratoplasty*); posteriormente, Gorovoy introdujo la disección laminar con microqueratótomo, designada DSAEK (del inglés *Descemet Stripping Automated Endothelial Keratoplasty*). En 2006, Melles desarrolló la técnica de DMEK (del inglés *Descemet Membrane Endothelial Keratoplasty*), en la cual solo se trasplanta el complejo EDM del donante, con un grosor de aproximadamente 15 µm. En 2009, Busin introdujo la técnica de DSAEK ultra-fino (UT-DSAEK), en la cual el injerto donante es preparado con microquerátotomo linear o con *double-pass* para obtener un grosor de injerto < 130 µm, y verificó resultados superiores a los de la DSAEK "convencional" en agudeza visual, complicaciones y supervivencia de injerto. [2] En 2018, Cheung desarrolló una técnica para obtener injertos con grosor < 50 µm designada DSAEK nano-fino (NT-DSAEK), [3] cuyos resultados son comparables con los de DMEK. [4]

Indicaciónes por queratoplastía laminar endotelial

Desde su introducción, la EK se ha convertido en la técnica *gold standard* en el tratamiento de enfermedades del endotelio corneal, siendo la técnica de trasplante corneal más practicada en un gran número de centros especializados. La EK está indicada en pacientes con patología o disfunción primaria o secundaria del endotelio corneal, incluyendo distrofias endoteliales (pe, distrofia de Fuchs, distrofia polimorfa posterior), queratopatía bullosa post-quirúrgica (pe, pseudofaquica, afáquica, tras cirugía de glaucoma o tras vitrectomía), síndrome iridocorneoendotelial, insuficiencia endotelial post-traumática, endoteliitis vírica (pe, virus de la familia *herpesvirus*) o fallo endotelial tardío tras queratoplastía. [1,5-7] Nuestro grupo ha demostrado que la DMEK es segura y efectiva en pacientes con fallo tardío de queratoplastia penetrante (PK, del inglés *penetrating keratoplasty*) [8] y en pacientes con DMEK previas, [9] y Arnalich-Montiel *et al.* han demostrado que la DSAEK es segura y efectiva en pacientes tras DMEK. [10] La EK estará contra-indicada en casos de patología endotelial con fibrosis estromal y subepitelial, en donde el paciente podrá obtener más beneficio visual con una PK. [5,6]

Las principales ventajas de la EK en comparación con la PK son las siguientes: [1,5-7]

- Cirugía en ojo "cerrado" (incisión corneal o escleral pequeña), en lugar de una cirugía "a cielo abierto";
- Rehabilitación visual más rápida;
- Menor alteración refractiva, ausencia de astigmatismo irregular y mayor previsibilidad de la toricidad corneal;
- Menor riesgo de rechazo endotelial de injerto (y sin riesgo de rechazo epitelial o estromal);
- Mejor calidad de vida relacionada con la visión.

En ojos faquicos, se puede hacer EK, pero la progresión de la catarata puede acelerarse tras la misma. En un candidato a EK con catarata, generalmente preferimos hacer la cirugía de catarata antes del trasplante (*staged surgery*) pero es posible hacer una cirugía combinada de cirugía de catarata e implante de lente intraocular (LIO) con EK ("cirugía triple"), con buen perfil de eficacia y seguridad. Respecto a la LIO, los principales aspectos a considerar son: 1) preferir lente intraocular monofocal asférica, porque la EK crea asfericidad negativa; 2) la DSAEK produce un cambio hipermetrópico, por lo que la selección de la LIO deberá tener como objetivo refractivo entre -0.75 y -1.50D; 3) preferir una LIO hidrofóbica, porque las LIO hidrofílicas tienen mayor riesgo de opacificación por deposición de hidroxiapatita. [5]

En ojos con polo anterior patológico (pe, afaquia, aniridia, ojos con LIO de cámara anterior, ojos con sinéquias anteriores, ojos con dispositivos de drenaje de glaucoma) y en ojos vitrectomizados, la EK es técnicamente más compleja y los riesgos de pérdida posterior del injerto, de pérdida endotelial precoz y de fallo tardío son mayores, y la decisión entre DSAEK o DMEK no es consensual. Pese a que la DSAEK tenga menor complejidad técnica y mayor experiencia que la DMEK en la mayor parte de los centros, hay evidencia creciente de que la DMEK en estos casos produce resultados favorables. [5]

Técnica quirúrgica y protocolo de profilaxis de rechazo inmunológico de injerto

El tejido donante de EK puede ser preparado en el quirófano, pero la tendencia es la preparación de tejidos en banco de ojos por técnicos especializados. Los botones donantes de EK habitualmente son más grandes que los de PK, con 8.5-9.0 mm de diámetro; lentículos demasiado grandes pueden causar sinéquias periféricas y pérdida endotelial por contacto irido-corneal, así como una mayor incidencia de rechazo. [5]

La mayoría de los pacientes puede ser operados de DSAEK o DMEK con anestesía local, pero el tipo de anestesia depende de la experiencia del cirujano y de las comorbilidades del paciente. Los pasos comunes en las cirugías DSAEK y DMEK son los siguientes: [5]

1) Marcaje epitelial de la córnea receptora de la dimensión pretendida por el trépano, con violeta de genciana;
2) De una a tres paracentesis y formación de cámara anterior (CA) con mantenedor de CA o con viscoelastico;
3) Creación de la incisión principal limbar o corneal (3-5 mm para DSAEK y 2.4-3.5 mm para DMEK);
4) Descemetorhexis bajo aire (o viscoelastico), con gancho Sinskey inverso y pinza de *stripping*; en casos de edema corneal severo, el azul tripan puede facilitar la identificación de remanentes de Descemet del receptor, los cuales pueden dificultar la adherencia del injerto donante al estroma del receptor;
5) Inserción del injerto donante con inyector de lentículo DSAEK o DMEK;
6) Sutura corneal de la incisión principal, para reducir pérdidas del injerto o gas durante las maniobras de desdoblamiento y posicionamiento del injerto;
7) Desdoblamiento y centramiento del injerto con técnicas "*no-touch"*;
8) Aposición del injerto donante al estroma del receptor, con burbuja de aire o con gas SF6 en concentración de 20% no expansiva; [11] el SF6 20% es superior al aire con respeto a la tasa de desprendimiento del injerto DMEK y sin aumento de la toxicidad endotelial; [12]
9) Iridectomía periférica inferior, que puede ser realizada preoperatoriamente con LASER Nd: YAG.

Típicamente, al final del procedimiento la burbuja de aire llena 40-60% de la CA y la de SF6 unos 80%. El paciente es posicionado "*face-up"* y observado a la primera hora postoperatoria para garantizar que no ocurre bloqueo pupilar; sí la presión intraocular está elevada, se hace un cambio de aire-fluido. En la primera semana, el paciente es posicionado *"face-up"*, pero se puede posicionar la cabeza del paciente para direccionar la burbuja para áreas con riesgo de desprendimiento. [5] El protocolo postoperatorio habitual incluye antibioterapia tópica, un hipotensor ocular tópico durante 3 meses, y corticoterapia tópica

durante 6-12 meses, con o sin corticoterapia sistémica; estudios recientes sugieren que existe beneficio en mantener la corticoterapia tópica prolongada después del primer año postoperatorio. [13]

Resultados de queratoplastía laminar endotelial

La EK produce resultados visuales clínicamente significativos, con una rehabilitación visual rápida y contínua con el tiempo, la cual resulta del *remodeling* del estroma corneal. [9] Los resultados visuales están influenciados por la severidad y duración de la descompensación corneal (edema corneal) y por la presencia de comorbilidades. La agudeza visual (AV) media tras DSAEK es entre 20/34 y 20/66, y 38-90% de los pacientes tienen AV > 20/40 al primer año tras DSAEK. Tras DMEK, 97% de los pacientes obtiene AV >20/40, y 39-47% tiene AV ≥ 20/20. [1,14] No está establecido si la indicación primaria para EK se asocia a los resultados y supervivencia del injerto, pese a que bastantes autores hayan observado que los pacientes con distrofia de Fuchs tienen mejores resultados comparando con pacientes con queratopatía bullosa post-quirúrgica.

Complicaciones de queratoplastía laminar endotelial

Las complicaciones de la EK pueden ser: [1,5,6,14]

1) En la preparación del tejido donante: perforación corneal; creación de un lentículo de grosor no uniforme o con superficie estromal irregular; manipulación excesiva del tejido con pérdida de células endoteliales;

2) Complicaciones intraoperatorias:
a. Problemas con la manipulación del injerto: injerto inverso; manipulación excesiva del injerto donante con pérdida aumentada de células endoteliales y riesgo aumentado de fallo de injerto; expulsión del injerto o migración posterior del injerto;
b. Dificultad en mantener gas o aire en la CA, particularmente en ojos con lente de cámara anterior, ojos con defectos del diafragma iris-cristalino, ojos operados de glaucoma y ojos vitrectomizados;
c. Catarata iatrogénica o luxación de la LIO;
d. Hemorragia; la sangre o humor vítreo en CA dificultan el desdoblamiento del injerto y pueden acumularse en la interface receptor-donante;
e. Raramente, hemorragia supracoroidea y hemorragia expulsiva.

3) Complicaciones postoperatorias:
a. Bloqueo pupilar por la burbuja de gas o aire;
b. Complicaciones relacionadas con el injerto:
   i. fallo primario de injerto (desde 0-12.5% tras DMEK y 0-29% tras DSAEK); [5,16]
   ii. descentramiento o desprendimiento de injerto, que puede necesitar de reinyección de aire (*re-bubbling*) en casos de desprendimiento total de injerto DSAEK y de desprendimientos > 33% de injerto DMEK;
   iii. rechazo inmunológico;
   iv. fallo tardío secundario de injerto, el cual puede resultar de la pérdida de células endoteliales y descompensación corneal, o ser secundario a episodios de rechazo inmunológico, glaucoma, infección y a traumatismo o cirugía ocular;
c. Otras complicaciones: Glaucoma o progresión de glaucoma previo a la EK; cataractogenesis acelerada u opacificación de la LIO; queratitis, infección de la interfase receptor-donante, y endoftalmitis; *ingrowth* epitelial; cambio hipermetrópico; edema macular quístico.

Los meta-análisis y revisiones sistemáticas de DMEK y DSAEK han demostrado que:

- La DMEK produce una rehabilitación visual más rápida y mayor satisfacción visual que la DSAEK, con mejor AV a los 6 y 12 meses y con mayor número de pacientes con AV ≥ 20/25;

- La DMEK induce menos cambio hipermetrópico (0.75-1.50D tras DSAEK *versus* 0.03-1.20D tras DMEK) y astigmático que la DSAEK, así como menor grado de aberraciones de alto orden;
- El mayor grosor del injerto DSAEK influencia negativamente la AV tras DSAEK, y las UT-DSAEK y NT-DSAEK producen mejores resultados visuales y menos aberraciones de alto orden que la DSAEK convencional; [2,4] sin embargo, en el *DETECT Trial* (un estudio randomizado comparativo) la DMEK demostró resultados visuales superiores a la UT-DSAEK al primer año de seguimiento. [15]
- La DMEK tiene una menor tasa media de rechazo inmunológico que la DSAEK (1.9% vs 10%); [14]
- La tasa de *re-bubbling* por desprendimiento del injerto donante es menor tras DSAEK que tras DMEK (3-15% tras DMEK vs < 3% tras DSAEK);
- La pérdida de células endoteliales tras DMEK es comparable con la pérdida tras DSAEK (aproximadamente 32-39% en los primeros 6 meses tras EK, y después tiene un perfil linear con el tiempo con 48-59% de pérdida a los 5 años y 68-71% a los 10 años), y la pérdida endotelial a largo plazo tras EK es mejor que la pérdida endotelial tras PK observada en el *Cornea Donor Study*; [1]
- La probabilidad de fallo tardío del injerto a largo plazo es comparable entre DMEK y DSAEK (80-96% de probabilidad de supervivencia del injerto a 5 años y de 79% a los 10 años tras DMEK). [1,14,17] La supervivencia de injerto es menor en la presencia de comorbilidades oculares, particularmente glaucoma o cirugía de glaucoma. [14]

Perspectivas futuras

Actualmente, los principales desafíos en queratoplastía son la disponibilidad de tejido ocular donante y la pérdida de células endoteliales con fallo tardío de injerto. Existen múltiples estrategias actualmente en estudio para solucionar este problema:

- La utilización de un donante para múltiples receptores. En 2016, el grupo de Melles reportó la técnica de hemi-DMEK y en 2018 los resultados a un año, [18] y en 2018 demostró resultados favorables a los 6 meses de seguimiento con un solo cuadrante de DMEK (quarter-DMEK); [19]
- La ausencia de injerto donante. Shah describió por primera vez un caso de *stripping* de la Descemet sin inserción de injerto corneal (2012) y en 2016 Moloney demostró la eficacia y seguridad de esta técnica en pacientes con distrofia endotelial de Fuchs central, designada DWEK (del inglés *Descemet Stripping Without Endothelial Keratoplasty*) o DSO (del inglés *Descemet Stripping Only*); [20]
- La ingeniería de tejidos biológicos es posiblemente una alternativa más atractiva, con la síntesis de injerto endotelial o con la inyección de células de endotelio corneal humanas cultivadas en la cámara anterior. [5] Kinoshita *et al.* han demostrado que la inyección de células endoteliales cultivadas suplementadas con un inibidor de la Rho kinasa produjo ganancia visual y trasparencia corneal significativos a los 2 años de seguimiento en pacientes con queratopatía bullosa. [21]
- El tratamiento farmacológico de las enfermedades del endotelio corneal es prometedor. Los inhibidores de Rho kinasa promueven la migración celular, proliferación y supervivencia de las células endoteliales en individuos humanos, y podrán mejorar los resultados de la EK, de la DWEK/DSO y de las técnicas de ingeniería de tejidos. [5, 22]

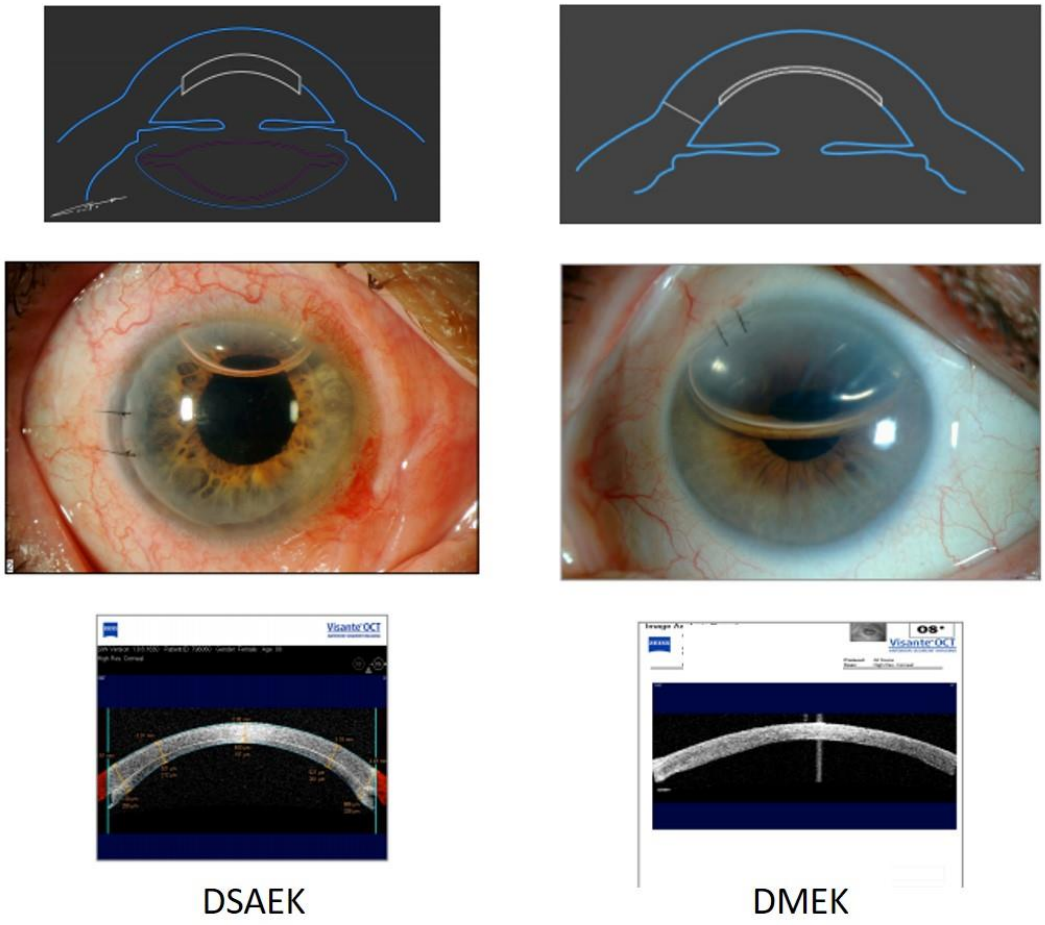


FIGURA 1 – Técnicas de queratoplastia laminar endotelial: DSAEK (*Descemet stripping automated endothelial keratoplasty*) y DMEK (*Descemet membrane endothelial keratoplasty*). Representaciones esquemáticas de DSAEK y DMEK (tope); fotografía de polo anterior de ojo tras DSAEK (medio, izquierda) y tras DMEK (medio, derecha); e imágenes de tomografía de coerencia óptica de polo anterior tras DSAEK (bajo, izquierda) y DMEK (bajo, derecha). Notad que el injerto DSAEK tiene mayor grosor que el injerto DMEK.

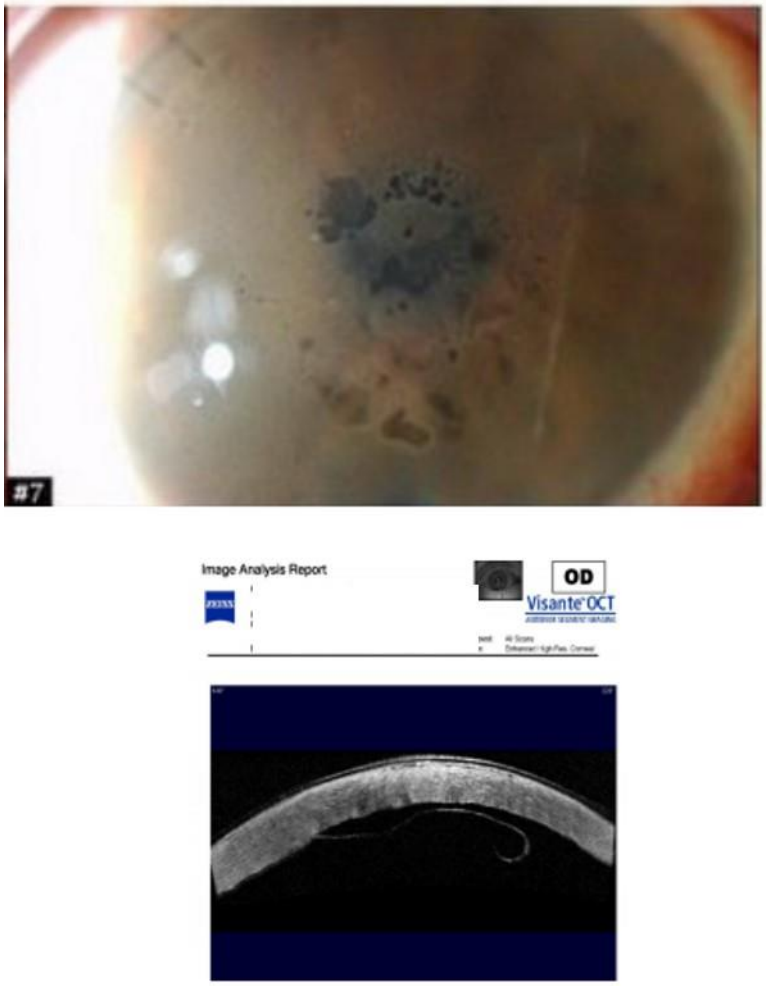


FIGURA 2 – Caso de fracaso primario de DMEK por injerto inverso, con edema corneal; desprendimiento del injerto DMEK en la OCT de polo anterior.

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PREGUNTA DE TEMA

1. Respecto a la queratoplastía laminar endotelial (EK), indica las afirmaciones verdaderas y falsas:

   a. El síndrome iridocorneoendotelial es una contraindicación para EK;
   b. La presencia de fibrosis estromal o subepitelial limita el potencial visual tras EK, y en estos casos podrá estar más indicada la realización de una queratoplastía penetrante;
   c. La mejoría de la función visual es un proceso contínuo tras DSAEK;
   d. La pérdida de células endoteliales tras DSAEK es superior a de la pérdida endotelial tras DMEK;
   e. Actualmente, solo son conocidos los resultados clínicos de técnicas de bioingenería con células endoteliales corneales humanas cultivadas suplementadas con inhibidores de Rho kinasa con un año de seguimiento.

RESUMEN

- La queratoplastía laminar endotelial (EK) es la técnica *gold standard* por el tratamiento de enfermedades primarias y secundarias del endotelio corneal, resultando en rehabilitación visual más rápida y menor riesgo de complicaciones que la queratoplastía penetrante (PK);
- La DSEK/DSAEK es técnicamente más simple que la DMEK y podrá estar más indicado en ojos con polo anterior complejo y en ojos vitrectomizados, asociándose a menor riesgo de desprendimiento de injerto;
- La DMEK produce resultados visuales superiores a la DSEK/DSAEK y tiene un menor riesgo de rechazo inmunológico;
- Las principales complicaciones de los injertos EK son el fallo primario, el desprendimiento de injerto con necesidad de *re-bubbling*, el rechazo inmunológico, el glaucoma, la progresión de catarata y el fallo endotelial tardío;
- La EK tiene un número creciente de indicaciones, incluyendo el fallo endotelial tardío tras PK o EK;
- Nuevas posibilidades en el tratamiento de las enfermedades del endotelio corneal incluyen la descemetorhexis sin injerto donante (DWEK/DSO), las técnicas con quadrantes de injerto DMEK (hemi- y quarter-DMEK), las técnicas de bioengenería de tejidos, y los tratamientos farmacológicos (inibidores de la Rho kinasa).

Reference: Güell, J.L., López, P., Gris, O., Manero, F., & Moura-Coelho, N. (2020) *DMEK en situaciones de afaquia: estrategias quirúrgicas. In: Cirugía Refractiva del Cristalino - Ponencia SEO 2020*.

Capítulo 11.8: DMEK en condiciones de afaquia. Estrategias quirúrgicas

Autores: José Luis Güell, Patricio López, Oscar Gris, Felicidad Manero, Nuno Moura-Coelho

Índice del capítulo

1.- Introducción
2.- Desarrollo
3.- Conclusión
4.- Bibliografía y Referencias

1. INTRODUCCION

En las últimas 2 décadas, las técnicas de trasplante corneal han tenido significativos y fundacionales avances, siendo el tratamiento de la disfunción endotelial corneal, fundamentalmente debido a distrofia de fuchs (FED) o queratopatía bullosa pseudofáquica (PBK) / afáquica, la más reciente en explotar y desarrollarse, con novedosas y variadas técnicas de queratoplastia endotelial que han venido a reemplazar su otrora solución terapéutica, el trasplante de espesor completo o Penetrating Keratoplasty (PKP) (1).

Este cambio en el paradigma, desde el reemplazo del tejido completo hacia la cirugía lamelar posterior, ha logrado menores tasas de rechazo post queratoplastia, permitiendo además preservar la integridad del globo ocular disminuyendo así las potenciales complicaciones intra-operatorias en cirugía a cielo abierto "open sky" (2). La Descemet´sMembrane Endotelial Keratoplasty (DMEK) es la técnica endotelial que va consiguiendo progresiva y sostenidamente más adherentes en los cirujanos de cornea, siendo la cirugía por incisión pequeña que ofrece recuperación más rápida (3) y mejores resultados visuales respecto a la Descemet´s Stripping Automated Endothelial Keratoplasty (DSAEK) (4), dado principalmente por el insignificante o nulo cambio inducido al estatus refractivo previo del paciente (33).

2. DESARROLLO

Desde su introducción en el año 2006 por Melles et al (17), una de las mayores ventajas descritas de la DMEK, además de la rápida recuperación visual y obtención potencial de la máxima agudeza visual mejor corregida (AVMC), es que posee la tasa más baja de riesgo de rechazo al compararla con todos los otros tipos de trasplante corneal (16). Junto a esto, gracias a lo estandarizado y depurado de sus técnicas actuales, también tiene menor índice de perdida de células endoteliales demostrado a 5 años de seguimiento cuando se compara con DSAEK (4,6), sin embargo, DSAEK sigue siendo la técnica de elección por muchos cirujanos de cornea5 en casos de limitada visualización del segmento anterior o cuando las condiciones anatómicas funcionales del ojo dificultan el despliegue y adhesión del lentículo endotelial, como lo es en casos de ojo vitrectomizados previamente, unicamerales, cirugía filtrante de glaucoma previa tipo trabeculectomía o dispositivo de drenaje y ojos afáquicos, esta última motivo de la presente revisión.

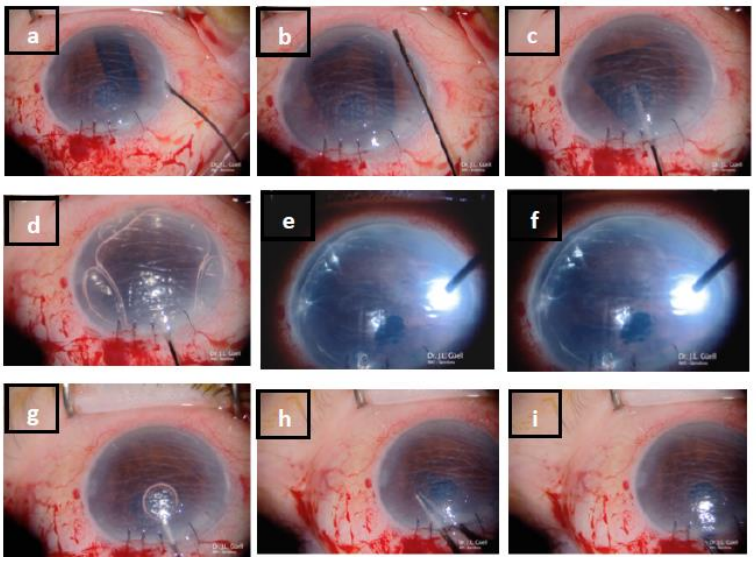
La DMEK ha sido reportada ocasionalmente en ojos afáquicos (15,18,19) como lo describen los artículos de Price et al y Vasquez et al entre otros, siendo realizada principalmente, pero no

exclusivamente, en casos en que el diafragma lente-iridiano ha sido restaurado con implante secundario de lente intraocular (LIO) (15) en el mismo acto quirúrgico o en un tiempo previo.

La queratoplastia endotelial tipo DMEK requiere algunas condiciones mínimas para su óptima ejecución (15), dentro de las cuales destacan la necesidad de transparencia corneal relativa, bicameralidad ocular con presencia de diafragma lenticular (LIO o cristalino), factibilidad de miosis pupilar y conservación relativa de morfología del segmento anterior, todas características necesarias para realizar adecuadamente la descemetorhexis bajo aire, fluido o visco elástico ocular (OVD) según preferencia, poder visualizar y manipular correctamente la posición del lentículo inyectado en cámara anterior (CA) y finalmente, para poder ejecutar la descemetopexia neumática bajo aire y/o gas a concentración iso-volumétrica (hexafloruro de azufre: SF6 al 20% o perfluoropropano: C3F8 al 14%) del injerto, maniobra clave para asegurar la adherencia del mismo al estroma posterior receptor, lo cual puede verse frustrado desde un inicio o minutos-horas después de la formación de la burbuja de aire/gas en CA, debido a una fuga precoz de la misma hacia cámara posterior (CP) o segmento posterior, siendo este el motivo por el cual algunos autores describen tanto la técnica de infusión vía pars plana, otros la inyección dual de gas en CA y en cavidad vítrea, así como la técnica de la doble burbuja en CA; una sobre y otra bajo el injerto, todas maniobras coadyuvantes a la hora de afrontar una cirugía DMEK en ojos afáquicos vitrectomizados (21,22).

Así, ante un paciente en afaquia, que requiera una queratoplastia endotelial por distrofia de fuchs o queratopatía bullosa por ejemplo, si se toma la decisión de realizar una DMEK (6,8,14,15,20) en busca de una recuperación visual rápida, máxima agudeza visual potencial o minimizar el riesgo de rechazo, teóricamente se deberá analizar si el segmento anterior del globo ocular cuenta con las condiciones mínimas morfológicas antes descritas, intentando evitar así complicaciones como lo muestran la Figura 1 (letras a-b-c-d-e-f-g-h-i) que, aunque con experiencia, poco frecuentes, pueden presentarse.

Figura 1:



Superado esto y tomada la decisión de realizar un DMEK en un paciente en afaquia, nos encontramos con 2 posibles escenarios a la hora de abordar la técnica:

A.- Corrección transitoria de la afaquia en conjunto con la DMEK:

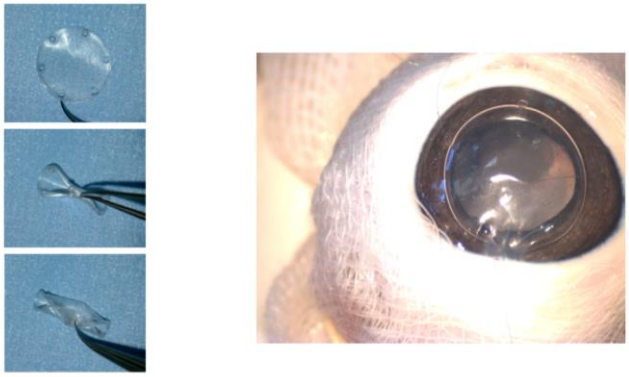
En el 2018 Yoeruek et al. (20), publicaron una nueva técnica para DMEK en ojos vitrectomizados, usando una lamina (lente) hidrofílica de metacrilato con orificios en su periferia, la cual genera un ambiente de doble cámara, actuando como mecanismo de diafragma temporal en CA que permite el despliegue del injerto y posterior taponamiento con aire/gas23 sin el riesgo de colapso del globo. La cirugía DMEK se realiza en forma estándar hasta que, tras la descemetorhexis y posterior extracción del endotelio enfermo, se implanta la mencionada lamina en CA, ejerciendo función de diafragma, continuando luego con la inyección del injerto DMEK y maniobras ulteriores de forma tradicional para lograr el despliegue, centrado y pexia de la lamela injertada, finalizando con la extracción del lente de metacrilato intra-cameral, por la misma vía.

En este grupo de corrección transitoria de la afaquia, también esta descrita la utilización de un lente tipo “ICL” (Implantable Collamer Lens) o “IPCL” (Implantable Phakic Contact Lens) como plataforma temporal que permita dividir la CA de la CP, para así facilitar el despliegue del injerto intra-cameral al permitir el aplanamiento de la cámara, evitar su caída y/o luxación a CP o cavidad vítrea y generar un ambiente hermético camerular, que permita mantener la burbuja de aire/gas inyectada in situ, la cual favorece la neumatopexia y evita su desprendimiento los primeros minutos y horas. Allan y cols (6) describen esta técnica, tras realizar la descemetorhexis y extracción del endotelio enfermo, implantando transitoriamente un lente EVO+ Visian ICL de

-8.00D en CA previa inyección de OVD tipo cohesivo, desplegándolo sobre el iris y apoyándolo a nivel del ángulo camerular, sirviendo de andamiaje y barrera transitoria para las maniobras que permiten pegar la lamela de DMEK. Una vez asegurado este punto, se procede al lavado cuidadoso del OVD intra-cameral, utilizando una cánula manual co-axial de irrigación/aspiración tipo Simcoe, contando así con las condiciones necesarias para luego proceder al implante de la lamela de DMEK, despliegue, centrado y posterior adhesión, pudiendo formar entonces la burbuja de aire manteniéndola por 5 minutos, para luego proceder a rellenar la cámara nuevamente con OVD conservando una burbuja de aire pequeña superior que sirva de protección para el injerto, extrayendo así con pinza endo-ocular el lente "ICL", maniobra que debe ser controlada y sutil, para evitar manipular accidentalmente el injerto. Finalmente, se procede a aspirar el OVD, rellenar y lavar con solución salina balanceada (BSS) la cámara y reformar la burbuja de aire/gas a un tamaño que permita la adecuada cobertura de todo diámetro de la lamela injertada, habiendo realizado previamente unairidectomía / iridotomía periférica a inferior para evitar el bloqueo pupilar secundario.

Presentándose como una tercera opción potencial de corrección transitoria de la afaquia, nuestro grupo comenzó el año 2017 un proyecto en conjunto con la empresa Ophtec (Figura 2), diseñando un implante con el objeto de darle hermeticidad anatómica al segmento anterior durante los procedimientos en que fuese necesario, como por ejemplo la cirugía DMEK. El implante de polysiloxane (una silicona hidrofóbica), el mismo material flexible con el que construyen las lentes "Artiflex", permite una fácil inserción y extracción a través de una incisión de 2 milímetros (mm), disponiendo además de unos orificios periféricos que facilitan su manipulación intra-cameral y actúan preventivamente a modo de iridectomía/iridotomía durante el periodo de taponamiento con aire/gas. Actualmente estamos en espera de recibir el permiso de la Agencia Europea (EMA) para su utilización clínica.

Figura 2: Proyecto "ongoing" con empresa Ophtec BV: Observar la permanencia de la burbuja en CA en un ojo afáquico de cadáver

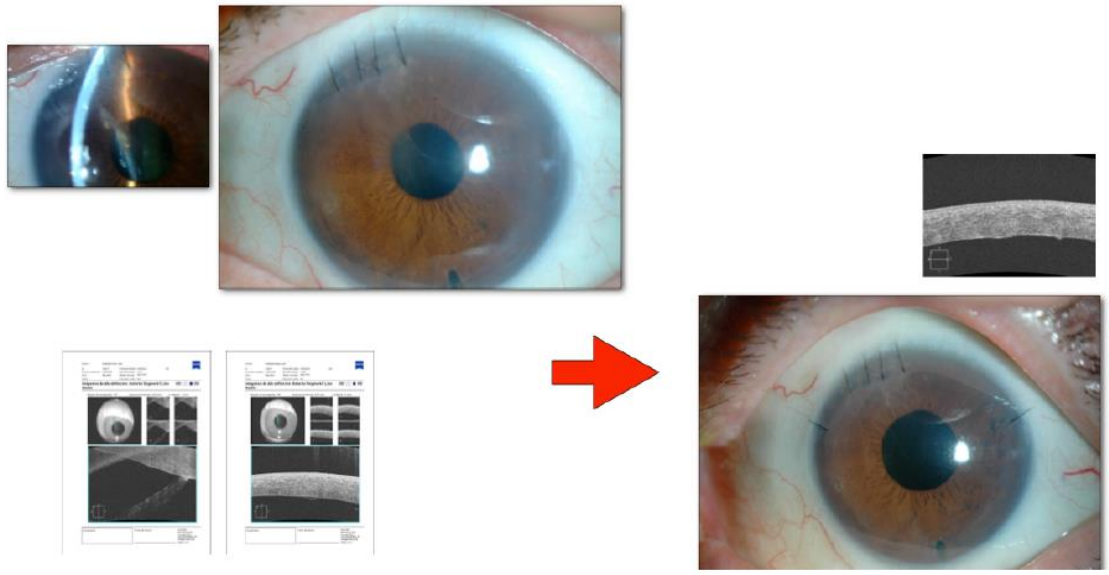


B.- Corrección definitiva de la afaquia en conjunto con la DMEK:

En este grupo, teóricamente las opciones dependen de la presencia o ausencia de adecuado soporte capsular en conjunto con la preferencia y familiaridad del cirujano con la plataforma de LIO a utilizar. En presencia de adecuado soporte capsular remanente, cualquier LIO hidrofóbico de 3 piezas inyectado al sulcus o monopieza inyectado al saco capsular con captura anterior o reversa de óptica es una opción para resolver la condición de afaquia, tras lo cual puede continuarse con la cirugía tradicional de DMEK. Relevante es destacar aquí la importancia en que la plataforma de lente a elegir sea idealmente hidrofóbica, dado que su contraparte; la hidrofílica de acrílico, presenta alta tendencia a la opacificación definitiva de su óptica24 cuando, tras la DMEK, esta entra en contacto con la burbuja de aire/gas, la cual se ha demostrado que "in vitro" induce una cristalización evaporativa (calcificación) del fosfato de calcio en la superficie y sub-superficie de la LIO (29,30,31,32), generándose un deposito granular distribuido con un patrón circular generalmente, que opacifica la lente de forma irreversible, como lo describió por primera vez Khan y Muhtaseb el 2011. Esta opacificación también está reportada sobre lentes hidrófobas aunque con mucho menor frecuencia.

En ausencia de adecuado soporte capsular, además de la pertinente y prolija realización de vitrectomía anterior automatizada, necesaria para evitar complicaciones derivadas de la maniobra de implante a elegir (Figuras 3 y 4); las opciones van desde LIO de CA de apoyo angular (7) o de soporte iridiano tipo iris-claw (8), este último ya sea enclavado pre o retro pupilar (14), LIO suturado a iris, LIO suturados a esclera asistido o no por adhesivo tisular (9, 11), hasta LIO fijado a esclera ya sea tipo fijación intraescleral de hápticas descrita por Chin Yamane (26,27) o fijación intraescleral 4-flanged descrita recientemente por Canabrava (28).

Figura 3: Imágenes a izquierda muestran fibra vítrea adherida a la incisión tras DMEK en ojo pseudofáquico con implantación 2ª a sulcus tras cirugía previa complicada con ruptura capsular posterior. Imágenes a derecha muestran el resultado tras realizarvitrectomía anterior y reinyección de aire2 semanas post DMEK.

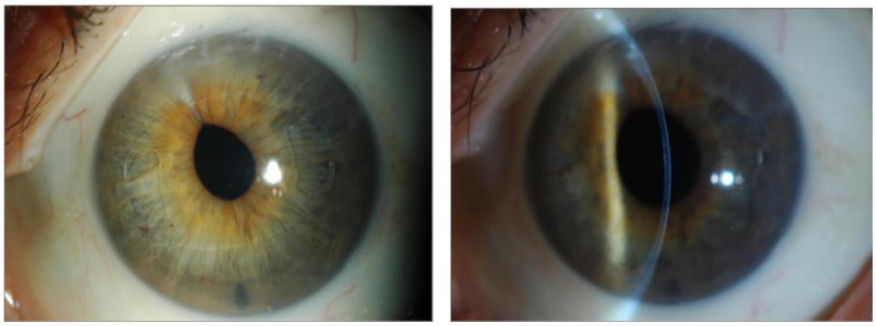


Todas estas opciones, conllevan riesgos de posibles complicaciones derivadas de la localización definitiva del lente y la dificultad en su ejecución, quedando a criterio del cirujano el tipo de técnica a elegir, teniendo siempre en consideración que por tratarse de una cirugía combinada de implante/recambio de LIO más queratoplastia endotelial, se debe priorizar evitar el daño potencial a mediano y largo plazo al endotelio injertado que afecten la sobrevida del mismo.

En nuestra experiencia, la utilización de una LIO "Artisan"afáquica de anclaje iridiano pre-pupilar tiene la ventaja sobre el resto por ser siempre una opción quirúrgica en estos casos (Figura 4), independiente de la presencia o ausencia de soporte capsular, la cual además de lograr solucionar el tema de la compartamentalización de forma definitiva actuando como diafragma que previene el paso del aire/gas desde la CA a la CP, permite mejorar refractivamente la ametropía generada por la condición de afaquia en forma bastante predecible y consistente, siendo una técnica muy eficaz y segura por la calidad de sus resultados visuales y baja incidencia de complicaciones intra y postoperatorias reportadas (11,12,13). Así entonces, una vez implantado y enclavado el lente y tras proceder al cierre de la incisión limbar o escleral de 5.2 a 5.5mm con sutura nylon 10-0, se continua con la realización de la cirugía de DMEK estándar igual que en un paciente pseudofáquico previo con la respectiva iridectomía/iridotomía periférica para evitar el bloqueo pupilar secundario tras la inyección de aire/gas. Gonnermann y cols (14) describen una técnica muy similar, diferenciándose de nuestra propuesta sólo en que realizan el anclaje iridiano a nivel

retropupilar y sin iridectomía periférica profiláctica (ya que fijan la LIO con su concavidad hacia arriba), logrando una significativa mejoría de la AVMC y una rápida recuperación visual, no obstante, consignando el mayor desafío técnico en el manejo de la burbuja de aire y el despliegue del injerto de endotelio luego de inyectada en CA, en comparación con la técnica estándar de DMEK.

Figura 4: DMEK en paciente con lente Artisan de afaquia pre-pupilar.



Finalmente, cabe resaltar que, Muraine y cols (34) proponen recientemente una nueva técnica de DMEK en pacientes afáquicos y anirídicos (Figura 5), que permite la realización de una queratoplastia endotelial, sea cual sea el aspecto de la CA, sin ningún tipo de soporte (temporal o permanente), realizándola con relativa sencillez y alta seguridad.

Figura 5 (A, B, C, D): Técnica de Marc Muraine y cols.

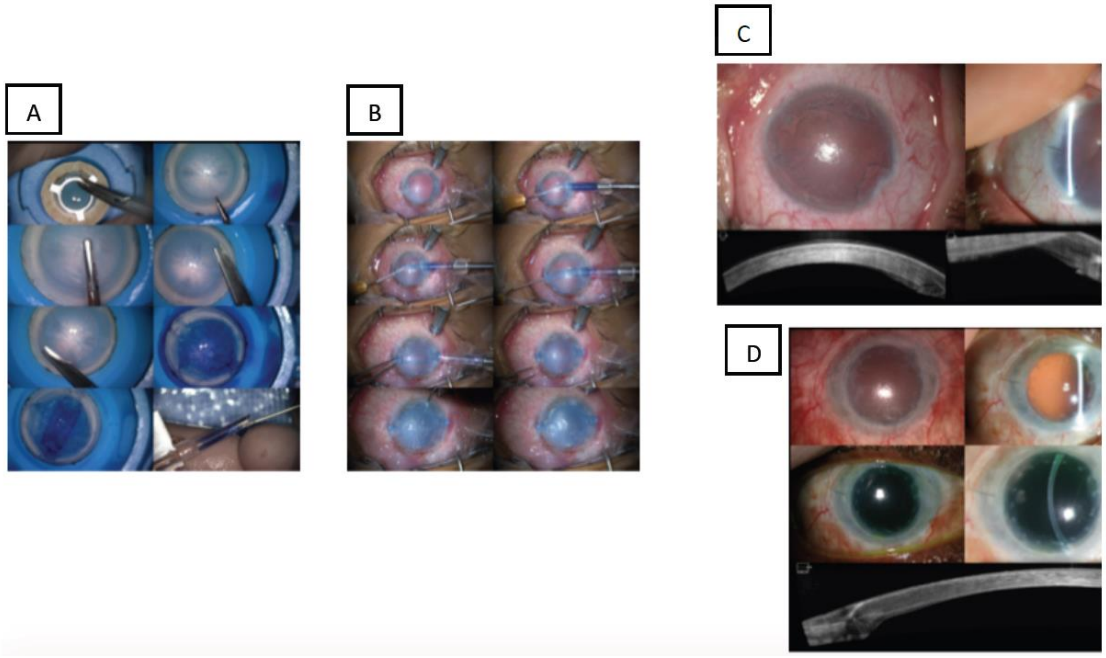


Figura 5 A:Preparación del injerto endotelial

A1: trepanación superficial de 8 mm botón corneo-escleral con endotelio hacia arriba.

A2 y A3: la córnea es invertida y puesta en una CA artificial con el endotelio hacia arriba. Trepanación superficial es realizada con una espátula justo debajo de la membrana de Descemet.

A4 y A5: separación del injerto con tijera vanas.

A6: injerto endotelial, de grosor 30 a 50 μm teñido con azul de tripan

A7 y A8: injerto endotelial, enrollado con cara endotelial dentro, es introducido en cartridge del inyector.

Figura 5 B:Implantación en paciente en afaquia post trauma

B1: paciente con aniridia parcial

B2 a B6: injerto endotelial es introducido en la CA con aguja acondicionada. Ambas pestañas del injertose mantienen en incisiones corneales para evitar que injerto caiga hacia la cavidad vítrea

B7 y B8: injerto es desplegado por inyección de una burbuja de aire

Figura 5 C: Implantación en paciente en afaquia y aniridia post trauma

Aspecto pre operatorio y post operatorio a 3 meses

OCT a 7 días post operatorio

Figura 5 D:Implantación en paciente en afaquia y aniridia post trauma

Aspecto del pre operatorio y post operatorio a 2 meses

OCT a los 2 meses.

3. CONCLUSION

La queratoplastia endotelial tipo DMEK es “per se” una técnica altamente desafiante y laboriosa ya en condiciones ideales, la cual se convierte en un desafío de gran magnitud y complejidad en casos de pacientes en afaquia y aniridia asociado a su disfunción endotelial (FED o PBK) correspondiente, esto dado principalmente por la dificultad en el despliegue y posterior fijación del injerto endotelial a su lecho estromal receptor. Los resultados exitosos publicados a la fecha, si bien escasos, nos evidencian variadas técnicas para su abordaje, contemplando la mayoría, la instalación de un diafragma “pseudo lenticular” que permite la hermeticidad de la CA para la ejecución del DMEK. Consideramos que la experiencia particular de cada cirujano y equipo de cornea, junto a la realidad local y condiciones del paciente, nos permitirá decidir cual es el mejor caso en donde aplicar una técnica u otra.

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Impact of COVID-19 on Corneal Transplantation: First *EuCornea Education Webinar*

Impacto da COVID-19 na Cirurgia de Transplantação Corneana: Primeiro *EuCornea Educational Webinar*

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KEYWORDS: Eye Banks; Corneal Transplantation; first *EuCornea Educational Webinar*; COVID-19; SARS-CoV-2

The ophthalmic scientific community has been put to test throughout the COVID-19 disease pandemic, and the several, successful virtual scientific meetings and webinars have demonstrated the great impact of social media in scientific communication.[1] In 11th March 2020, the World Health Organization declared the COVID-19 outbreak a pandemic. One year later, the ophthalmologist community "e-gathered" to attend the first *EuCornea Educational Webinar* in 11th March 2021, which addressed the subject of corneal grafting and COVID-19.

During the pandemic, four main issues regarding risk management have been recognized: 1) the risk to sufficiency and sustainability of donor corneas, 2) the risk regarding viral status of the donor tissue, 3) the risk to eye bank and ophthalmology department staff, and 4) the risk to corneal graft recipients. Rethinking eye surgery and ocular tissue processing and preservation strategies was essential from the outset, as the ocular surface harbours proteins which allow SARS-CoV-2 virus entry into ocular surface cells, and as the virus RNA has been detected in conjunctival swabs of patients with COVID-19. In addition, a spectrum of ocular manifestations has been described in patients with COVID-19, although the incidence of conjunctivitis and other ocular complications appears to be low.[2]

In response to the COVID-19 pandemic, Ophthalmology departments and Eye Banks worldwide were placed in lockdown or reorganized into "COVID-19 units" in the early phase of the pandemic, and since then have resumed their activity at variable rates. Early in the pandemic, eye banks adapted quickly, and reduced procurement led to an excess of available tissue, with the problem of limited tissue shelf time. In Europe, the number of procurements decreased by 38%-68% between March-May 2020, compared with the mean of the two previous years.[3] Later, with the progressive adaptation of both eye banks and cornea departments, increased pressure has been imposed on eye banks due to increased deferrals. Importantly, during the webinar it was highlighted that these changes were felt more strongly in smaller eye banks compared with higher-volume eye banks. Several strategies have been proposed to address these issues, including storage of dehydrated corneas (which may last up to 6 months in storage) particularly for anterior lamellar keratoplasty[4,5]; the use of hemi- and quarter-DMEK grafts[5]; and the use of one donor cornea for multiple recipients.[6]

Additional complexities in transplantation during the pandemic include questions regarding donor and recipient screening. It is still not definitive whether donor corneal tissues harbour the SARS-CoV-2 RNA, with conflicting findin-

gs in the literature,[7-9] including findings of both RNA and the envelope and spike proteins in one study,[9] and positive findings in asymptomatic donors in another study.[10] From 588 donors from the Veneto Eye Bank Foundation without medical evidence nor epidemiological links to COVID-19 cases, only three cases (0.5%) tested positive for SARS-CoV-2 in nasopharyngeal rt-PCR samples, of which two corneal specimens yielded SARS-CoV-2 RNA.[10] During the webinar, speakers pointed out that positive genomic tests may not relate to viral replicability, as cases with detectable SARS--CoV-2 RNA in corneal tissue have low small genomic RNA expression, which suggests low or no viral replicability; and Dr Thuret mentioned that no bilateral positive cases were found, although unilateral infection may be possible. Besides, Dr Thuret found high inter-individual variability of ACE-2 and TMPRSS2 expression, meaning donors with positive nasopharyngeal PCR may not have corneal positivity. Despite these controversies, it is generally considered that the overall risk of transmission of SARS-CoV-2 through keratoplasty may be low, but that further research is warranted to assess the rate of SARS-CoV-2 transmission. Dr Dickmann pointed out that this is supported by the fact that there is no known transmission of other respiratory viruses in corneal grafts. Even so, until further data is available, most international guidelines avoid donor tissues from patients with COVID-19 disease. Current EEBA guidelines state that patients with active COVID-19 disease at time of death must be excluded from corneal donation, but that people with a positive PCR >14 days before death may be eligible 2 weeks after complete recovery and symptom-free at the time of death.[11] Post-mortem nasopharyngeal PCR testing is therefore critically important,[9,12] particularly in individuals with unknown status prior to death.[11] According to the webinar speakers, further testing (including Western blot testing) likely has no added value to the validation of PCR results.

Regarding donor ocular tissue preparation, although concerns have arisen for potential ocular infectivity and infection of collection team staff,[13] with adequate protective measures this risk may be very low.[8] Since it appears that SARS-CoV-2 viral replication and its lytic activity restricts to epithelia, removal of all conjunctival tissue and corneal epithelial removal with povidone-iodine (PVI) is a crucial step in donor preparation.[9] Although further evidence is required to demonstrate its efficacy on SARS-CoV-2 in corneal tissues, coronaviruses in inanimate surfaces appear to be rapidly inactivated following PVI exposure; the European Center for Disease Control considers PVI exposure to be validated for enveloped virus, and the current EBAA Medical Standard requires double exposure to PVI at the ocular surface before tissue recovery. However, eye banks and ophthalmologists must remain aware that PVI does not accomplish complete sterilization, nor does it eliminate the possibility of viral retention within ocular structures.[14]

It is recommended that patients undergo RT-PCR before keratoplasty and that PCR-positive patients are postponed, unless the emergent cases, in which all surgical staff should wear full protective equipment.[13] Dr Ponzin suggested that endothelial keratoplasty may be a safer procedure compared with penetrating keratoplasty, since the corneal endothelial layer lacks ACE-2 and TMPRSS2. The postoperative follow--up must take into account the possibility of the patient being infected with SARS-CoV-2, which may increase susceptibility for immune rejection episodes, possibly to viral induction of a proinflammatory state.[15] Finally, Dr Dickmann stated that COVID-19 vaccination is safe in corneal transplant patients. However, it may be advisable to increase immunosuppressive treatment in patients with corneal allografts undergoing COVID-19 vaccination, particularly in patients at increased risk of rejection such as patients with corneal regrafts; webinar speakers mentioned two cases of rejection episodes shortly following vaccination. Dr Dickmann suggested increasing topical steroids to 4 times daily 2 days before vaccination and for a period of 2 weeks, and highlighted the importance of keratoplasty patients to watch out for potential signs of graft rejection under the "RSVP" acronym for redness, sensitivity to light, vision blurring, and pain.

In conclusion, the first *EuCornea Educational Webinar* weaved sound considerations into corneal transplantation and eye banking during the COVID-19 pandemic. Key messages are that transplant activity during a pandemic should be fluid and tailored, with careful donor and recipient selection. International existing networks including EuCornea and the EEBA facilitate communication and foster cooperation to minimize the influence of the pandemic on donation and corneal transplantation activity. Prompt adaptation by eye banks and cornea departments allowed normalization of corneal grafting activity throughout Europe; that is, the "corneal transplantation chain" is rapidly adaptive, albeit at variable rates throughout Europe. With the appropriate measures for donor collection and preparation, and with careful perioperative protective measures, healthcare professionals and keratoplasty recipients likely have a low infectivity risk. Future challenges ahead will include the management of corneal patients undergoing COVID-19 vaccination, as well as further identification of potential donors among those with previous history of COVID-19 disease.

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REFRACTIVE ACCURACY AFTER CATARACT SURGERY AND DESCEMET MEMBRANE ENDOTHELIAL KERATOPLASTY




The potential use of premium IOLs in patients with Fuchs dystrophy who undergo a triple procedure.

BY NUNO MOURA-COELHO, MD, MMED, FEBO, AND JOSÉ L. GÜELL, MD, PHD

REFRACTIVE OUTCOMES AFTER DESCEMET MEMBRANE ENDOTHELIAL KERATOPLASTY + CATARACT/ INTRAOCULAR LENS TRIPLE PROCEDURE: A FELLOW EYE COMPARISON

Augustin VA, Weller JM, Kruse FE, Tourtas T[1]

Industry support: None

ABSTRACT SUMMARY

A retrospective fellow eye analysis evaluated whether the refractive spherical equivalent shift (RSES) after Descemet membrane endothelial keratoplasty (DMEK) combined with phaco cataract surgery and IOL implantation (ie, triple procedure) in the second eye followed the RSES in the first eye. Investigators analyzed the 3-month outcomes of 127 patients with Fuchs endothelial corneal dystrophy (FECD; Krachmer grade 5) and comparable mean preoperative data, including spherical equivalent, BCVA, central corneal thickness, and posterior corneal curvature. The RSES was calculated as the difference between the manifest refraction spherical equivalent and the residual refractive error predicted by optical biometry with the Haigis formula (ie, target refraction). All patients received a monofocal, spherical, one-piece hydrophilic IOL with a hydrophobic surface.

Three months after surgery, the visual and anatomic outcomes were comparable between both eyes. The mean hyperopic RSES was 0.98 ±0.89 D, with a mean difference between the first and second eyes of 0.49 ±0.43 D in a paired analysis. The difference between mean RSES in the first and second eyes, however, did not reach statistical significance.

DISCUSSION

In the study by Augustin et al,[1] the RSES after DMEK ranged from -1.51 to +3.72 D, highlighting the relative refractive unpredictability of the corneal procedure. DMEK is superior to Descemet stripping endothelial keratoplasty and penetrating keratoplasty in terms of refractive outcomes, but changes of 1.00 D or more in the target refraction occur in as many as 35% of DMEK eyes.[2] The main issue with refractive accuracy in FECD eyes is an overestimation of corneal power, largely due to posterior corneal changes that disrupt the corneal anterior-posterior relationship.[2,3]

Disease stage was similar in both eyes in the study by Augustin et al.[1] Using the first eye as a reference for the second eye appeared to be a valid strategy, and it was extrapolated from crystalline lens surgery on non-FECD eyes. Notably, although this approach showed good predictability, graph interpretation suggested that significant interocular RSES differences still occurred in 20% of patients.

It is generally accepted that refractive stability is reached 3 months after DMEK, but many eyes experience refractive and topographic changes thereafter.[2] An enhancement after DMEK should be postponed until refractive and topographic stability is confirmed. The decision to provide an enhancement should be made on a patient-by-patient basis.[4] The risk of opacification is greater with hydrophilic versus hydrophobic IOLs; if the opacification is significant, an IOL exchange may be required, which puts the DMEK graft at risk.[5]

STUDY IN BRIEF

- A retrospective study evaluated the refractive shifts experienced by patients with Fuchs endothelial corneal dystrophy who underwent a bilateral triple procedure (Descemet membrane endothelial keratoplasty combined with cataract extraction and IOL implantation). The refractive shifts observed in the first and second eyes were comparable.

WHY IT MATTERS

The refractive shift after the triple procedure is difficult to predict. The study indicated that the refractive outcome of the first eye may be used to predict the refractive target of the second eye.

REFRACTIVE ACCURACY IN EYES UNDERGOING COMBINED CATARACT EXTRACTION AND DESCEMET MEMBRANE ENDOTHELIAL KERATOPLASTY

Campbell JA, Ladas JG, Wang K, Woreta F, Srikumaran D[6]

Industry support: J.G.L., Principal (Advanced Euclidean Solutions); D.S., Consultant (Alcon)

ABSTRACT SUMMARY

The retrospective cohort study evaluated the accuracy of five IOL formulas (Hoffer Q, SRK/T, Holladay 1, Barrett Universal II [BUII], and Haigis) in 86 FECD eyes that underwent the triple procedure and for which there was at least 3 months of postoperative follow-up. The investigators analyzed the accuracy of the formulas using a thick lens equation based on anterior and posterior corneal radii and corneal thickness acquired preoperatively with Scheimpflug corneal topography.

The Hoffer Q, SRK/T, Holladay 1, and BUII formulas produced a mean hyperopic error, and the Haigis formula produced a mean -0.10 D myopic error. The Haigis and the BUII formulas exhibited the highest and the lowest refractive predictability, respectively (Table). Corneal power modification yielded a significantly lower corneal power than optical biometry measurements and significantly improved accuracy with all but the Haigis formula.

STUDY IN BRIEF

- A retrospective cohort study of patients with Fuchs endothelial corneal dystrophy who underwent cataract extraction and IOL implantation combined with Descemet membrane endothelial keratoplasty (ie, triple procedure) found a mean hyperopic error for the Hoffer Q, SRK/T, Holladay 1, and Barrett Universal II formulas and a mean myopic error for the Haigis formula. Corneal power modification using topographic data resulted in significantly lower mean absolute errors with all but the Haigis formula.

  Hyperopic errors had weak but significant positive correlations with preoperative posterior corneal curvature and posterior asphericity.

WHY IT MATTERS

When a thick lens equation modification of corneal power was used, the accuracy of most of the evaluated IOL formulas in eyes that underwent the triple procedure improved significantly. The Haigis formula may yield the highest refractive accuracy in this patient population.

DISCUSSION

Corneal topography/tomography (and probably corneal densitometry) is essential to understand the impact of posterior corneal changes in patients with FECD. The study by Campbell et al demonstrated relative refractive unpredictability after DMEK.[6] The mean postoperative manifest refraction spherical equivalent was -0.29 D, but the range was -4.25 to +2.25 D. Moreover, 40% of eyes ended up hyperopic, and only 50% to 70% of eyes were within ±1.00 D of the target refraction using optical biometry corneal power measurements.

Incorporating corneal topographic/tomographic parameters, including asphericity, corneal posterior curvature, and central-peripheral thickness relationship, into IOL power determination may improve refractive results after DMEK. IOL formulas that account for central corneal thickness may be affected by the limitations inherent to isolated measurements of this parameter in FECD eyes because changes in corneal thickness after DMEK contribute to the RSES.[3] The Haigis and other formulas using corneal power modification improved refractive accuracy, but newer formulas (eg, seven-variable vergence, AI, and ray-tracing) may improve it further.[7] Studies addressing DMEK refractive outcomes have placed emphasis only on spherical equivalent. Up to one-third of eyes, however, may experience a change in cylinder that is greater than 1.00 D,[2] although DMEK produces small mean changes in astigmatism.[8]

Refractive unpredictability after DMEK poses challenges for the use of toric and presbyopia-correcting IOLs in eyes that undergo the triple procedure.[9,10] Comparisons of staged surgery (ie, cataract and IOL surgery followed at a later date by DMEK) versus the triple procedure yield conflicting results.[11] Attractive alternatives include the following:

TABLE. COMPARISON OF REFRACTIVE OUTCOMES BY FORMULA AND BETWEEN OPTICAL BIOMETRY CORNEAL POWER VERSUS CORNEAL POWER MODIFIED BY CORNEAL TOPOGRAPHY*

Formula	Method	Mean error (D)	MAE (D)	MedAE (D)	Within ±0.50 D	Within ±1.00 D
Hoffer Q	OBCP vs TMCP	+0.66 vs +0.24	1.02 vs 0.82	0.91 vs 0.62	28% vs 37%	60% vs 65%
Holladay 1	OBCP vs TMCP	+0.59 vs +0.17	0.97 vs 0.82	0.79 vs 0.62	29% vs 40%	64% vs 69%
SRK/T	OBCP vs TMCP	+0.51 vs +0.10	0.93 vs 0.85	0.76 vs 0.63	31% vs 45%	65% vs 72%
Barrett Universal II	OBCP vs TMCP	+0.90 vs +0.48	1.16 vs 0.90	1.05 vs 0.75	21% vs 35%	49% vs 66%
Haigis	OBCP vs TMCP	-0.10 vs -0.52	0.85 vs 0.90	0.63 vs 0.74	41% vs 34%	69% vs 63%

*Adapted with permission from Campbell et al[5]

Abbreviations: MAE, mean absolute error; MedAE, median absolute error; OBCP, optical biometry corneal power; TMCP, topography-modified corneal power

- Phakic DMEK followed by cataract surgery and the implantation of a presbyopia-correcting IOL[12]; and
- The use of a Light Adjustable Lens (RxSight), which can theoretically correct up to 2.00 D of residual sphere and up to 3.00 D of cylinder.[13] ■

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Safe and effective: DMEK after penetrating keratoplasty

New developments and update in **lamellar surgery**

BARCELONA Corneal allogeneic transplantation has a long track record of efficacy, and a good prognosis for graft survival – reported graft survival rates are up to 90 percent at five years and up to 72 to 80 percent at ten years after penetrating keratoplasty (PKP)[1,2], and reported cumulative survival rates after endothelial keratoplasty (EK) range from 75 to 96 percent at five years and up to 79 percent at ten-year follow-up[3-6].

However, late endothelial graft failure (LEGF) and immune rejection (IR) are the main causes of corneal graft failure after PKP as well as EK. Although the endothelial cell (EC) loss during the first postoperative year is higher for EK grafts compared with PKP grafts, long-term data shows that EC becomes higher in PKP grafts three to five years after surgery, and this difference is progressively more significant with longer postoperative follow-up.[4,7,8]

In these cases, repeat keratoplasty (regrafting) is very effective and safe; and indeed, regrafting is one of the main indications for PKP and EK at present, representing approximately 15 to 20 percent of all PKPs and seven to 15 percent of keratoplasties performed worldwide.[9,10] However, eyes undergoing repeat PKP are high-risk cases, with increased risk of IR, increased risk of postoperative complications such as glaucoma, and decreased mean survival; and these risks increase for each regraft performed.[11,12]

Descemet's membrane endothelial keratoplasty (DMEK) can rescue a failed PKP graft. It has been shown to be surgically feasible and effective, improving visual acuity.[13] Importantly, performing a DMEK under a failed PKP graft is associated with a significantly lower risk of IR compared with repeat PKP, as much as a 43 percent risk reduction in a recent meta-analysis.[14] Nevertheless, DMEK grafts under PKP may have increased risk of rebubbling, rejection and graft failure compared to eyes undergoing DMEK for other indications.[15,16]

Eyes with failed PKP grafts

DMEK should be considered as an alternative in eyes with failed PKP grafts without significant stromal scars and with an acceptable refractive profile, especially in cases with high-risk features such as corneal neovascularization or history of IR episodes.

However, these eyes are complex cases for DMEK. Usually, an equal or slightly undersized EK graft is recommended, to avoid the host-donor interface of the PKP graft. Some surgeons do not perform descemetorhexis of the failed PKP graft, but it is likely that descemetorhexis is beneficial to improve DMEK graft adherence.

Some strategies can be adopted to improve visualization of the PKP Descemet's membrane and of the DMEK graft in the anterior chamber, including epithelial debridement, performing the descemetorhexis under air, performing a deeper staining of the DMEK graft, and the use of intraoperative OCT. It is important to ensure a well centered DMEK graft, and a large gas fill of the anterior chamber is advised (leaving an 80–90% gas fill).

Eyes with failed EK grafts

DMEK is also an effective alternative in eyes with failed EK grafts. In cases of failed Descemet Stripping (Automated) Endothelial Keratoplasty (DSEK/DSAEK), DMEK results in quick visual recovery and significant improvement in visual acuity.

A comprehensive literature review has shown that eyes undergoing DMEK for failed DSEK/DSAEK grafts may reach higher levels of visual acuity compared to eyes that undergo repeat DSEK/DSAEK, with comparable rates of rebubbling, IR and failure.[17]

Repeat DMEK is also feasible and safe, leading to significant, early, and continuous visual improvement.[18] In these cases, removing the failed graft under air improves the visualization of potential graft remnants. The visual outcomes after repeat DMEK are comparable to those of virgin eyes undergoing DMEK, but the time between DMEK failure a regrafting likely influences the visual outcomes, with longer times negatively influencing visual prognosis.[17] The complication rates are comparable between redo DMEK and primary DMEK eyes, but of note, repeat DMEK grafts may have a slightly higher risk of IR compared with primary DMEK eyes and may be at a higher risk of failure.

Finally, DMEK is feasible and effective for failed EK grafts in eyes with significant comorbid conditions, but these eyes have increased surgical complexity and may be at a higher risk for graft failure[19]; proposed risk factors for DMEK regraft failure include indication for primary DMEK surgery, complicated anterior segments, prior glaucoma surgery and need of rebubbling.[20].

Eyes with previous DALK

DMEK may also be an alternative to rescue eyes with previous deep anterior lamellar keratoplasty (DALK) grafts and endothelial failure. This is an infrequent scenario, with scarce reports in the literature that suggest performing a 0.25–mm undersized descemetorhexis of the DALK graft is feasible and successfully improves visual acuity, but has a high risk of rebubbling and a high rate of EC loss.[21] In conclusion, DMEK is a safe and effective rescue technique in eyes with failed corneal grafts.

DMEK under failed PKP grafts leads to good visual results and, more importantly, has a significantly reduced risk of rejection compared with repeat PKP. DMEK after failed DSEK/DSAEK is more likely to achieve better visual outcomes compared to repeat DSEK/DSAEK.

Repeat DMEK is safe and effective, with visual outcomes comparable to those of primary DMEK if regrafting is not significantly delayed. However, despite the advantages of DMEK in these eyes, some cases of failed PKP are not amenable to DMEK, particularly eyes with significant astigmatism or stromal opacities; in eyes with failed EK grafts, PKP might be considered in eyes with suspected significant posterior stromal irregularities which may hinder DMEK graft adherence; and DMEK in the setting of previously failed corneal allografts are likely a "not so low-risk" setting subgroup of DMEK patients who have a higher risk of graft rejection and graft failure. In these cases, long-standing immune rejection prophylaxis with a topical corticosteroid is strongly recommended to improve graft survival. ■



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New developments and update in lamellar surgery
08.09.2023 13:45-13:55; Room: A2

OCT eye imaging at home?

Inexpensive laser could **increase access to OCT imaging,** helping to catch eye problems early

VIENNA Researchers have shown that a vertical cavity surface emitting laser (VCSEL) diode, which is commonly used in telecommunications and lidar applications, could offer a less expensive light source for swept-source optical coherence tomography (OCT). This advance could lead to ophthalmologic OCT systems that are practical for use outside the ophthalmology clinic, even at home.

Although single-mode VSCELs usually operate using a constant current, the researchers varied the current to achieve the changes in the wavelength, or color, needed for swept source OCT. In "Optics Letters", the researchers describe their custom OCT setup that incorporates a VCSEL and advanced post-processing algorithms. They used the setup to obtain full-eye scans on a healthy volunteer.

In their study, the researchers set out to see if a VCSEL diode could be used in place of the expensive swept-source laser. While VCSEL diodes typically produce a laser output beam at a certain well-defined wavelength, if the diode's operating temperature changes, the output wavelength will also change.

"Our idea was to leverage an unwanted effect of wavelength shifting with temperature to make these diodes usable for OCT," said research team member Milana Kendrisic, from the Medical University of Vienna in Austria. "We deliberately induce a temperature change by ramping up the driving current in a short time to high values beyond its original specifications. This is followed by a cooling period to avoid deterioration of the diode material, which lets us tune the diode over a broader bandwidth than is otherwise possible."

"Even though commercial swept sources have larger spectral bandwidths, we showed that even the small range we achieved with a VCSEL is sufficient to perform OCT," explains Kendrisic. "Although VSCEL-based systems have some limitations in terms of image quality, they still have the potential to expand access to diagnostic imaging and improve patient care in areas where traditional OCT systems may not be available or affordable," the first author of the publication states. ■

Source: Optica 2023; Kendrisic M et al. Thermally-tuned VCSEL at 850 nm as a low-cost source alternative for full eye SS-OCT. Opt Lett 2023;48(11):3079–3082.

COVID-19: An Ophthalmologist's Perspective

COVID-19: A Perspetiva do Oftalmologista

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ABSTRACT

In just one hundred years, the world has been through five pandemics. Lessons of the past have not prevented a new virus from being responsible for a fifth wave of deaths worldwide, even with scientific advances and the rapid response of societies that, for the most part, anticipated the political and economic response. A century after the end of the Spanish Flu (1918/19), in December 2019, the world has watched the beginning of the second pandemic of the 21st century, coronavirus disease 2019 (COVID-19) caused by a new severe acute respiratory coronavirus syndrome-2 (SARS-CoV-2).

The eye can not only be the entry point for coronaviruses, but also a target organ. Conjunctivitis, uveitis, vasculitis, retinitis and optic neuritis have all been documented in animal models studies.

In this article, we review the possible roles of the visual system/ocular tissues as an entryway, and the potential ophthalmic manifestations of human SARS-CoV-2 infections. This review article will also highlight the most effective ways for protecting and preventing the spread of the virus.

KEYWORDS: COVID-19; Coronavirus Infections; Disease Outbreaks; Eye Diseases; Eye/virology; Ophthalmology; Pandemics; SARS-CoV-2

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RESUMO

Em apenas cem anos, o mundo registou 5 pandemias. As lições do passado não evitaram que um novo vírus fosse responsável pela quinta vaga de mortes a nível mundial, mesmo com os avanços científicos e a rapidez de resposta das sociedades que, na sua maioria, se anteciparam à resposta política e económica. Passado um século do final da Gripe Espanhola (1918-19), em dezembro 2019, regista-se o início da segunda pandemia do século XXI, a coronavirus disease *2019 (COVID-19) provocada por um novo coronavírus (CoV),* severe acute respiratory syndrome coronavirus - 2 *(SARS-CoV-2).*

O olho poderá ser não só a porta de entrada dos CoV, como também um dos órgãos-alvo do mesmo. Conjuntivite, uveíte, vasculite, retinite e nevrite ótica foram documentadas em modelos animais.

Neste artigo, fazemos uma revisão dos possíveis papéis do sistema visual/tecidos oculares como porta de entrada, bem como das possíveis manifestações oftalmológicas da infeção humana por SARS-CoV-2. Este artigo de revisão também destacará as normas mais eficazes de proteção e evicção de propagação do referido vírus.

PALAVRAS-CHAVE: *Coronavírus; Doenças dos Olhos; Infeção por Coronavírus; Oftalmologia; Olho/*virology*; Pandemia; Síndrome Respiratória Aguda Grave; Surtos de Doença*

INTRODUCTION

HISTORICAL BACKGROUND: 100 YEARS OF PANDEMICS

The current COVID-19 pandemic is still far from being equated with other global public health crises. However, it worries both the authorities and scientific community, which have long tried to anticipate a new pandemic, and the population, which remains the key to flatten the pandemic's progression curve.

The H1N1 virus pandemic, widely known as Spanish flu, which began in 1918 and ended in 1919, killed more than 50 million Europeans, North Americans and Asians, taking many more lives than World War I.[1] Since then, 4 more deadly pandemics (1957, 1968, 2009 and 2019-20) have been recorded by the World Health Organization (WHO). Asian influenza, caused by an influenza A virus of the subtype H2N2, victimized about 2-4 million people in 1957-58, affecting mainly children of Southeast Asia. The Hong Kong flu (1968-69), caused by another influenza H3N2 virus, currently still in circulation, has a lower mortality rate (due to its genetic similarities to the Asian flu), with around 1 million deaths reported.[2] The H1N1 virus again emerged in 2009 as a combination of the swine, avian and human influenza viruses, originating in Mexico. It was responsible for what was initially called the swine flu pandemic and later type A flu. This pandemic made more victims in Argentina, Brazil and Mexico, with two hundred thousand deaths having been reported, and 62% to 85% of those being in people under 65 years.[3]

A century after the end of the Spanish flu, the second pandemic of the 21st century started in December 2019 in the city of Wuhan, China, due to a new coronavirus responsible for a severe acute respiratory syndrome (SARS). On the 30th of January of 2020, the WHO has declared this disease as the sixth public health emergency of international concern (PHEIC),[4] following the 2009 H1N1 pandemic (2009), the 2014 polio outbreak in the Middle East (2014), the Ebola outbreak in West Africa (2014), the Zika outbreak in Brazil/South America (2016), and the 2019 Ebola outbreak in the Democratic Republic of Congo (2019).[5]

On the 11th of February of 2020, the WHO announced a new name for the epidemic disease caused by 2019--nCoV: coronavirus disease (COVID-19). Regarding the virus itself, the International Committee on Taxonomy of Viruses has renamed the previously provisionally named 2019-nCoV as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[6]

One month later, on 11th March 2020, the WHO declared COVID-19 as the second pandemic of 21st century.[7]

This new pandemic has spread across the globe rapidly, affecting 2 108 897 people in the world as of the 16th of April 2020.[8]

METHODS

We searched the PubMed and Google Scholar databases to identify articles published up to 16th April 2020, using the following key terms: "COVID-19", "coronavirus", "pandemic". In addition, we manually searched the reference lists of most primary articles and reviewed articles.

CORONAVIRUS - VIROLOGY AND PROPOSED PATHOGENIC MECHANISMS

Coronaviruses (CoV) are enveloped, positive stranded RNA viruses that belong to the *Coronaviridae* family and the order Nidovirales.[9] The CoV have been known to affect birds and mammals.[10] Public opinion became aware of CoVs after the outbreak of the severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003.[11] The SARS-CoV outbreak was responsible for more than 8000 infected patients and 774 deaths in 26 countries.[12]

In 2012, a new CoV variant was detected in Saudi Arabia which was responsible for the coronavirus-related Middle Eastern respiratory syndrome (MERS-CoV). MERS-CoV was isolated in the same year[13] and has been responsible for more than 850 deaths.[14] Of the 2223 confirmed cases in the MERS-CoV laboratory reported to the WHO, 415 were healthcare professionals, representing more than a third of all secondary transmission[15] and a fifth of all cases. Both severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) are caused by coronaviruses.

The entry of SARS-CoV in human host cells is mediated mainly by an angiotensin-converting enzyme 2 receptor (ACE2-R),[16] which is expressed in the epithelium of human airways, in the lung parenchyma, vascular endothelium, kidney cells and intestinal cells.[17] However, the presence of ACE2-R is neither enough nor necessary to make host cells susceptible to infection. For instance, in some scientific studies, endothelial cells that express ACE2 and human intestinal cell lines were not infected with SARS-CoV,[18] while some cells with very low levels of ACE2 expression, such as hepatocytes[19] or neuronal cells,[20] could also be infected with SARS-CoV.

The respiratory involvement of human CoV has been clearly established since the 1960s. Data reported in scientific literature has also demonstrated that, similar to other human viruses, CoV have naturally neuroinvasive and neurotropic capacities, with potential neuropathological consequences in genetically or otherwise susceptible individuals, with or without additional environmental insults. The presence of CoV in the human central nervous system (CNS) is now a recognized fact, either as a result of hematogenous or transneural spread.[21]

Increasing evidence shows that CoVs can first invade peripheral nerve endings and then gain access to the CNS. Trans-synaptic transfer has been well documented for other CoVs, such as hepatitis E virus (HEV),[22,23] and avian bronchitis virus.[24,25]

It is known that interleukin 6 (IL-6) has neurotrophic and neuroprotective effects and can increase the permeability of the blood-brain barrier.[26] A high level of IL-6 leads to progressive neurological disorders with neurodegeneration and cognitive decline.[27] Although elevated serum levels of IL-6, interleukin 8 (IL-8) and monocyte chemoattractant protein 1 (MCP-1) in patients infected with SARS and MERS have been illustrated,[28-30] there are studies in which there are no significant increases in the serum levels of these cytokines but they become significantly accumulated in the cerebrospinal fluid of patients with CoV infection.[31]

Moreover, Arbour *et al* showed that human CoV (HCoV) can infect human astrocytes and microglia in primary cultures and can acutely and persistently infect immortalized human glial cells.[32]

Severely affected patients are more likely to develop neurological symptoms, including headache, disturbances in consciousness and paresthesia, than patients with mild or moderate disease.[33] Autopsy reports have revealed brain tissue edema and partial neuronal degeneration in deceased patients with COVID-19.[34] Another study has reported a case of viral encephalitis, caused by a new CoV with confirmation of the presence of SARS-CoV-2 in cerebrospinal fluid by genome sequencing.[35] In addition, an increasing number of patients with COVID-19 report a sudden loss of smell or taste. Therefore, anosmia and dysgeusia are likely to be seen in patients with COVID-19.[36,37]

In addition to hematogenous dissemination, a second form of viral dissemination to the CNS is through the neuronal retrograde pathway.[38] After an intranasal infection, both HCoV-OC43[39] and SARS-CoV[40] have been shown to infect the respiratory tract in mice and to have neuroinvasive behavior.[41,42] Interestingly, several viruses, including the neurotropic strains of murine coronavirus (MuCoV) and the mouse hepatitis virus (MHV) reach the CNS through the olfactory nerve.[43] However, Brann *et al* concluded that mouse and human olfactory sensory neurons do not express two key genes needed for SARS-CoV-2 entry, ACE2 and transmembrane serine protease 2 (TMPRSS2). On the other hand, olfactory support epithelial cells and stem cells express these two genes, as well as cells in the nasal respiratory epithelium. These findings suggest possible local mechanisms through which SARS-CoV-2 infection can lead to anosmia or other forms of olfactory dysfunction.[44]

CORONAVIRUS AND THE EYE

Although COVID-19 is transmitted mainly by respiratory droplets and direct contact, a recent report has raised the question of whether ocular surfaces could be a potential site for SARS-CoV-2 invasion, in part, due also to virus hepatitis murine aerosols.[45]

As previously mentioned, many studies have described the binding of SARS-CoV-2 to human ACE2-R, resulting in the invasion of host cells.[46,47] In the eye, the ACE2-R is expressed mainly in the posterior tissues, namely in the retinal pigment epithelium. Whether ACE2 /ACE2-R expression and activity are present in the ocular surface cells of humans and rabbit models (including cornea and conjunctiva) remains controversial.[48]

The polymerase chain reaction (PCR) technique in human tears has been widely used by ophthalmologists to diagnose eye infections, especially of the *herpesviridae* family, such as the herpes simplex virus types 1,[49-51] the Epstein-Barr virus[52] or even adenovirus.[53] There is also evidence that some coronaviruses can occasionally cause conjunctivitis in humans. In fact, the human coronavirus NL63 (HCoV-NL63) was first identified in a baby with bronchiolitis and conjunctivitis.[54] Later, in a study of twenty-eight cases of children with confirmed HCoV-NL63 infection, 17% had conjunctivitis.[55]

Guan *et al* reported nine cases of conjunctival congestion in 1099 studied cases of COVID-19 positive patients.[56] However, other ocular manifestations of COVID-19 are still unknown and can include as increased conjunctival secretion, epiphora and decreased vision. In a study by Chen *et al* of 534 patients with COVID-19, twenty-five (4.68%) had conjunctival congestion and in three patients this was the initial symptom. That same study also found that ocular dryness, foreign body sensation and blurred vision were the three main eye symptoms in these patients (20.9%, 11.8% and 13.9%), which may be due to the fact that these patients spend much time using electronic devices.[57]

In another study with thirty patients, there was only one patient with conjunctivitis. Viral RNA was isolated in his tear fluid and conjunctival secretion twice. Its clinical signs were similar to a common viral conjunctivitis, with conjunctival congestion and watery discharge. The patient did not have severe fever or respiratory symptoms when his samples were collected. No viral RNA was detected in the tear fluid and conjunctival secretions of critically ill or common patients without conjunctivitis.[58] These findings have led to the speculation that the virus present in tears can reach the respiratory system through the nasolacrimal ducts.[59]

It is known that the virus can trigger other pathological processes in the eye besides conjunctivitis and keratitis. In fact, the herpes simplex virus and the varicella zoster virus have been implicated in acute retinal necrosis[60,61] and cytomegalovirus is capable of inducing retinitis in immunosuppressed individuals.[62] Degenerative changes in the retina have also been observed in Creutzfeldt-Jakob disease and in subacute sclerosing panencephalitis due to rubella infection.[63] Also, it is common for a viral or flu-like illness to precede Multiple evanescent white dot syndrome (MEWDS), acute posterior multifocal placoid pigment epitheliopathy (APMPPE) and acute macular neuroretinopathy, which led some to suspect of a viral etiology.[64,65] In addition, the MuCoV and the MHV, induce an acute and chronic eye disease in BALB/c mice.[66,67] In the early acute phase, 1 to 7 days after inoculation, mild retinal vasculitis is observed and in the second stage, on the 10th day and progressing for several months, retinal degeneration can be observed in the absence of vasculitis or inflammation. It is interesting that the development of the degenerative phase is controlled by a genetic predisposition of the host and it has been associated with the development of anti-retinal and anti-retinal pigment epithelium (RPE) autoantibodies.[68]

Murine coronavirus infections can be modified or regulated by several factors including virus serotype, route of inoculation, genetic and age or stage of development of the host.[69] In fact, the host's genetic context can influence the type and intensity of the immune response, the presence of cell membrane surface molecules used for viral adsorption and penetration, and the intracellular composition of the cell that allows viral replication.

In the retina, the RPE cell is a potent regulatory cell and appears to play a critical immune role, probably presenting foreign proteins, retinal proteins and viral RNA present in the infected cells to helper T cells.[70-73] Several studies indicate that MHV can cause acute and persistent infections in the central nervous system, such as acute necrotizing encephalitis followed by chronic CNS demyelinating disease.[74-76]

In fact, according to Bergmann *et al*, despite the T cell-mediated control of acute virus infection, host regulatory mechanisms, probably designed to protect the integrity of the CNS, contribute to the failure in eliminating the virus.[77]

Moreover, hypoxia, ischemia and edema may also be implicated in retinal vasculitis as reported in patients infected with Rift Valley fever virus[78,79] and West Nile virus.[78,80-82]

If observed, retinal vasculitis in CoV Infected patients may be due to a cytokine storm associated with elevated IL-6, which can lead to edema and increased permeability of vascular walls as proposed in cases of myocarditis.[83] In Portugal there are already unpublished reports of retinal vasculitis and a VI cranial nerve palsy in patients that tested positive for SARS-CoV-2.

STANDARDS FOR PROTECTING AND PREVENTING THE SPREAD OF SARS-CoV-2

Ophthalmologists examine patients at close distances and inadvertent physical contact with patients' eyes is almost inevitable. This is a potential hazard to healthcare workers given the close contact with the face, including the nose, mouth and the eyes of SARS patients. Therefore, particular care is advisable when examining any patient. There is a potential possibility of transmission to other patients with reusable eye equipment such as the Goldmann applanation tonometer, trial contact lenses, trial frames, and even reusable pinhole devices which come in close contact with the patient's eyes.[84,85]

According to Lian *et al*, no virus particles were detected in the tears and conjunctival secretions in patients without conjunctivitis.[86] However, the low abundance of the virus in tear and conjunctival secretions does not eliminate the risk of transmission through conjunctival tissue. For the same reasons, the use of contact lenses should be discontinued until the COVID-19 emergency comes to an end.

Moreover, the most commonly used noncontact tonometer for ophthalmologic examination, the air puff tonometer, forces an air puff during the examination, which produces a large amount of aerosols in the local area. Aerosols may be concentrated in the local air for a long time, and general alcohol wipe disinfection is ineffective, causing widespread concern in the field of ophthalmology.[87] The noncontact tonometer, ultrasound biomicroscopy, corneal confocal microscope, and others do not theoretically cause cross-infection.[88-91]

During an ophthalmological examination the use of adequate protections, including gloves, eye protection devices (eye shields), adequate protective masks (FFP2 and FFP3 or N95 and N99) and protective shields to be mounted on slit lamps is mandatory for community safety and to limit the risk of disease transmission between ophthalmologists and patients. Should the lack or incomplete availability of such devices be verified, ophthalmological practice ought to be suspended.[92,93]

CONCLUSION

The eye can be not only the entry point for CoV, but also one of its target organs. Conjunctivitis, uveitis, vasculitis, retinitis, optic neuritis and other neuro-ophthalmological diseases will be probably reported in the future.

Knowing that especially the most serious forms of COVID-19 infection have neurological semiology, we believe that concurrent neuro-ophthalmological findings are likely underdiagnosed and undervalued because this disease is life-threatening. We also believe that, in the future, and particularly in survivors of intensive care, there will be reports of neurodegenerative and demyelinating eye pathologies linked to the previous infection with SARS-CoV-2.

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Corneal endothelial failure

DMEK is the surgical treatment of choice

BARCELONA – Corneal allogeneic transplantation is, at present, the only available treatment modality for the treatment of corneal endothelial failure, which is the main indication for corneal transplantation worldwide.

Penetrating keratoplasty (PKP) has been superseded by posterior lamellar keratoplasty (PLK) techniques as the corneal allograft transplantation techniques of choice in this setting, due to increased safety of the procedure, superior topographic and tectonic results, faster visual recovery and rehabilitation, higher refractive predictability, lower rejection rates, and lower corneal endothelial cell (CEC) loss over the long term. Although PLK techniques were first described in 1956, worldwide adoption of early techniques was hindered by the technical difficulty of these procedures, until Busin described the use of the microkeratome to obtain the donor lenticule in 2000, and Melles et al. described the descemetorhexis technique in 2004, paving the way for development of Descemet stripping membrane endothelial keratoplasty (DSEK/DSAEK), and of Descemet membrane endothelial keratoplasty (DMEK) in 2006 (Fig. 1). Increasing evidence that graft lenticule thickness in DSEK influenced visual outcomes, later technical refinements in donor lenticule preparation by Busin et al. led to the appearance of ultra-thin DSAEK (UT-DSAEK), and later to predescemetic endothelial keratoplasty (PDEK) by Agarwal et al.

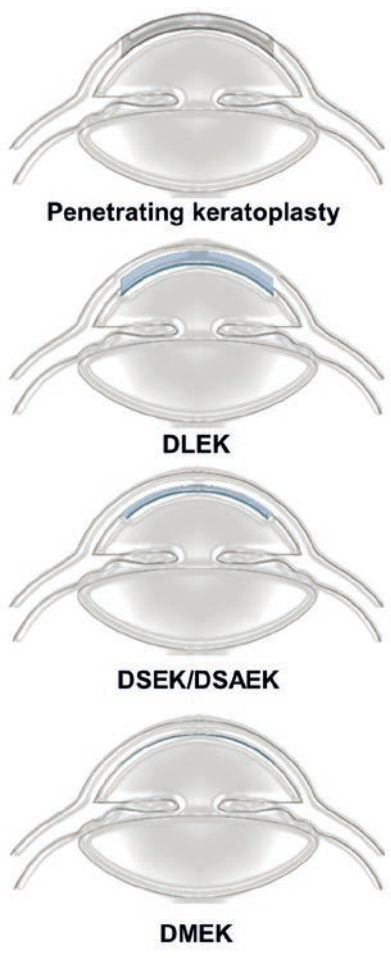


Fig. 1: Surgical techniques for the treatment of corneal endothelial failure
In PKP, the entire recipient's cornea is removed and replaced by a donor full-thickness corneal allograft, including epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelial cell layer. PLK techniques include all forms of corneal allograft transplantation in which only the posterior layers of the donor cornea (endothelial layer, Descemet's membrane, with or without posterior corneal stroma) are transplanted into the host. In DLEK, an early PLK technique no longer in use, a posterior lamellar disc composed of endothelium, Descemet's membrane and posterior stroma is manually dissected from the recipient cornea. In DSEK, the endothelial-Descemet's complex (EDM) is stripped from the recipient cornea, and is replaced with a donor allograft composed of EDM, plus posterior stroma of variable thickness using a manual dissection or automatic dissection with a microkeratome (DSAEK). In DMEK, the recipient's EDM complex is replaced only by donor Descemet's and endothelium.

Due to simpler graft preparation and manipulation, its surgical feasibility in complex eyes, and lower rebubbling rates, DSAEK has been more widely adopted worldwide in yester years compared with DMEK. However, and while the postoperative CEC loss and graft survival after DSAEK may be comparable to DMEK, DMEK has several advantages over DSAEK1-6:

(1) Earlier and better visual acuity, including a higher proportion of eyes reaching higher levels of visual acuity and lower levels of higher-order aberrations (HOAs); while this difference may be less marked with ultra-thin DSAEK, there is good quality evidence that DMEK is superior to this technique in terms of visual acuity and HOAs.
(2) Lower cumulative rejection risk, due to reduced alloantigen load. The cumulative rejection risk rates of DMEK are as low as four percent at ten-year follow-up, compared with an estimated ten percent rate after DSAEK.
(3) DMEK may be cost saving when compared with DSAEK, although the evidence is not definitive
(4) Regrafting in eyes with previous DMEK grafts likely produces superior visual outcomes compared with eyes with previous DSAEK grafts.

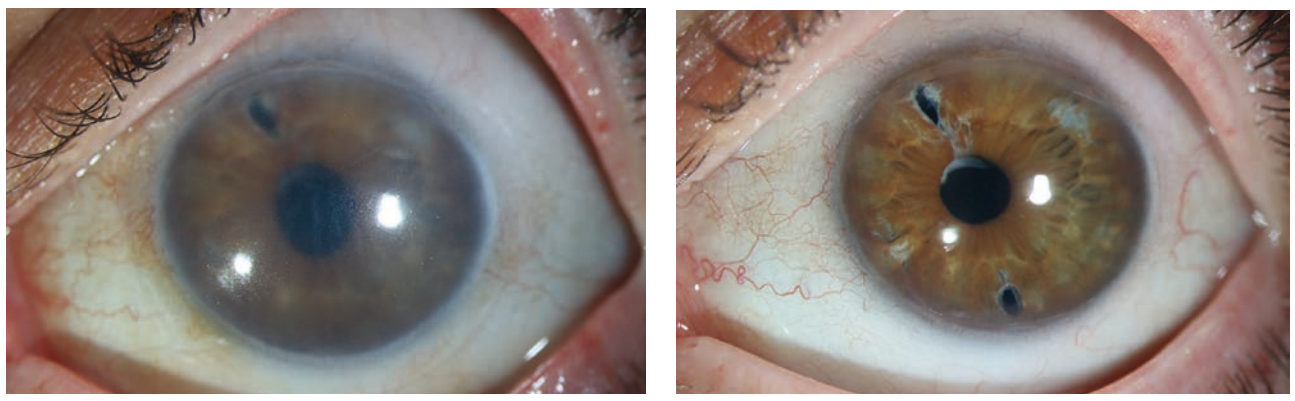


Fig. 2: Slit-lamp anterior segment photograph of an eye with bullous keratopathy (left), and the same eye one year after DMEK (right), with rapid clear cornea and visual recovery.

DMEK has demonstrated excellent long-term visual and anatomical outcomes, with 80 to 95 percent graft survival and less than four percent rejection rate after five to ten years of follow-up[3,5]. The main drawback of DMEK compared to DSAEK is increased re-bubbling rate. However, it remains uncertain that need of re-bubbling after DMEK affects outcomes adversely[7]. Besides, although the recipient posterior stroma's intrinsic properties likely influence graft attachment, re-bubbling rates after DMEK have decreased progressively, due to increased surgical experience, the use of sulfur hexafluoride 20 percent ocular endotamponade for graft attachment[8] and adequate postoperative positioning[9].

With the growing experience and number of DMEK surgeries performed worldwide, there has been an expansion of its indications to include complex eyes (eyes with glaucoma drainage devices, corneal decompensation due to phakic IOLs, eyes with pathological anterior segments, vitrectomized eyes). DMEK has demonstrated to be safe and effective in many complex eyes, albeit the increased surgical complexity and the higher risk of CEC loss and graft failure in these cases compared with Fuchs' endothelial corneal dystrophy (FECD) eyes[10]. DMEK has also shown to be feasible, safe and highly effective as a "rescue technique" in eyes with failed penetrating or lamellar grafts[11–13]. Finally, DMEK has emerged as a novel alternative to manage corneal complications, including LASIK interface fluid syndrome related to CEC failure and acute hydrops[14,15].

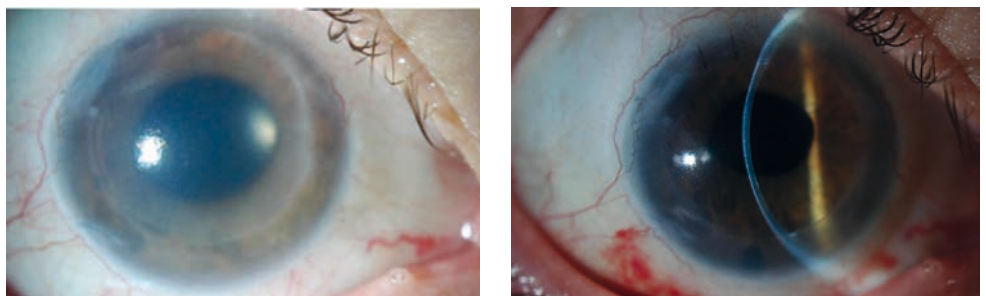


Fig. 3: A case of successful DMEK under a failed penetrating keratoplasty graft.

The high efficacy and safety profiles of DMEK are reflected in the continuously increasing trends in the USA, where the number of DMEKs have now matched the number of DSAEKs[16], in stark contrast with the data in the previous decade.

Donor corneas worldwide are available for one in 70 patients[17], and although partial donor tissue techniques have been proposed to optimize tissue availability, including hemi-DMEK and quarter-DMEK, these grafts have increased CEC loss and earlier graft failure compared with standard DMEK grafts. As such, novel therapeutic strategies for endothelial failure in the horizon will be directed towards tackling the issue of donor corneal tissue scarcity. Ongoing, early clinical investigations for managing endothelial failure include topical Rho-kinase inhibitors and novel surgical techniques, including Descemet's membrane stripping only (DSO or DWEK), acellular Descemet's membrane transplantation (DMT), gene therapies, injection of cultured CECs into the anterior chamber, bioengineered corneal tissue, and artificial endothelial keratoprosthesis. DSO has shown good visual results in cases of mild central non-decompensated cornea guttata after up to five years of follow-up, and in eyes where DSO fails, DMEK is still feasible[18]. The early trials of CEC intracameral injection have shown excellent outcomes up to five years after treatment[19,20], but larger data is needed; the ongoing IOTA trials will shed more light into this therapy. These novel techniques have shown promising results in early trials; however, they are still at a very early stage, and still lack the long-term results which already honor DMEK graft surgery. Optimization of corneal donor tissue and resources in the future will possibly include determining if a patient with FECD is a suitable candidate to these novel therapies (DSO, CEC injection therapy) or if they will require a standard DMEK graft; this "suitability" may perhaps be based on "genetic profiles" or "FECD sub-types" (e.g. presence of fibrillary layer) correlated with outcomes after these treatments[21, 22]. ■


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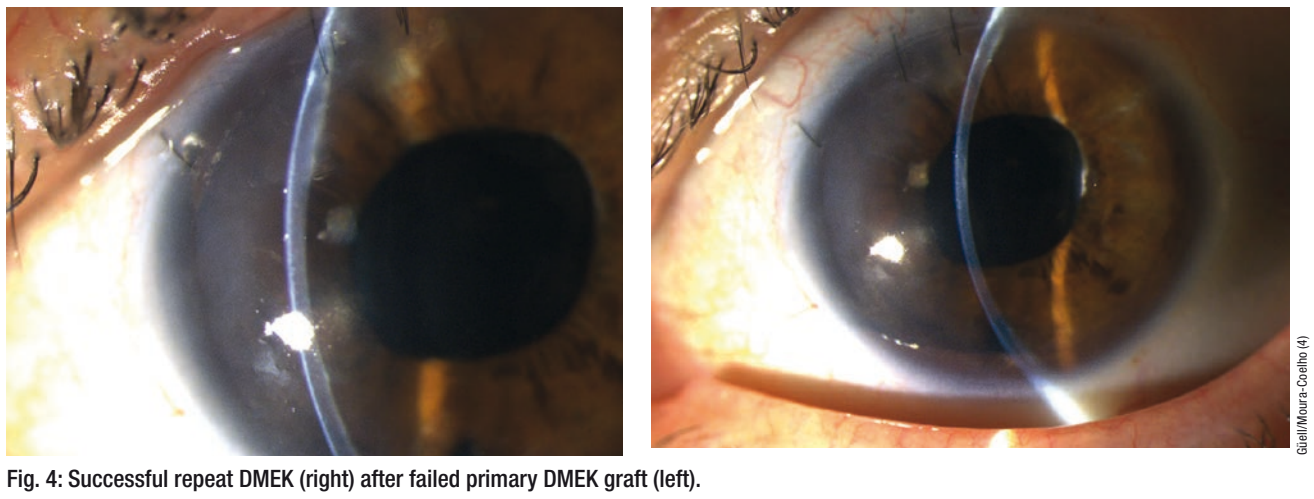

Güell/Moura-Coelho (4)

Fig. 4: Successful repeat DMEK (right) after failed primary DMEK graft (left).

References upon request.

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Main Symposium: Emerging Treatment Options for Corneal Endothelial Disease
16.09.2022 17:00–19:00, Room: Auditorium