



Descemet membrane endothelial keratoplasty in eyes with COL8A2-associated corneal dystrophy

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ABSTRACT

Purpose: The p.(Leu450Trp) COL8A2 mutation, associated with an early-onset corneal endothelial dystrophy, can result in bullous keratopathy within the first few decades of life. People with this condition frequently experience anterior corneal changes in keratometry as the disease worsens, which may potentially affect refractive error after endothelial keratoplasty. We describe outcomes of the first cases of Descemet Membrane Endothelial Keratoplasty (DMEK) for patients with known mutations in this gene.

Observations: Four eyes from two patients with COL8A2-associated corneal dystrophy underwent DMEK for this condition at a tertiary academic center. Preoperative and postoperative Scheimpflug imaging and manifest refraction was conducted. Mean central corneal thickness decreased from 713 μm preoperatively to 529 μm at one month. Despite long-standing corneal haze, all eyes reached between 20/20 and 20/30 best corrected visual acuity, and minimum postoperative central corneal thickness reached 482, 479, 479 and 533 μm . Refractive changes frequently occurred during the first postoperative year, with 3.6 D, 3.3 D, 3 D, and 0.8 D shifts in spherical equivalent taking place within this time period in the four eyes.

Conclusions and Importance: In two patients with the p.(Leu450Trp) mutation in COL8A2 who underwent DMEK, resolution of corneal edema resulted in centrally thin corneas and refractive shifts postoperatively. Despite chronic edema, excellent visual acuity was achieved in all eyes.

1. Background

The p.(Leu450Trp) mutation in COL8A2¹ is associated with, endothelial failure and markedly thickened Descemet membrane, resulting in peripheral microcystic edema and formation of bullae at a young age.² Ten-year progression data demonstrates a rapid increase in anterior corneal astigmatism due to such changes; in one pedigree, corneal edema was present by age 11 in one family member, and astigmatism increased by 5.1 diopters between age 38 and 43 in another family member due to bullous changes.³ Penetrating keratoplasty and Descemet stripping endothelial keratoplasty (DSEK) are treatments that have shown to be helpful,³ but outcomes of Descemet Membrane Endothelial Keratoplasty (DMEK) in eyes with this specific genetic variant have yet to be described.

Two simultaneous processes take place after Descemet Membrane Endothelial Keratoplasty (DMEK): post-operative thinning of the central

cornea, and decreased water content within the cornea as the edema resolves. Therefore, DMEK results in a range of refractive outcomes,⁴ but often averages out to a slight hyperopic shift. Notably, anterior corneal keratometry remains relatively stable after DMEK for mild Fuchs dystrophy.^{5,6}

In the cases described here, two people with a known genetic variant of early-onset Fuchs dystrophy experienced bullous keratopathy and underwent DMEK with cataract surgery at age 49 and 56. These are, to our understanding, the first cases of DMEK for people with known mutations in this gene.

2. Findings

2.1. Case 1

A 49-year-old woman presented with decreased vision over the

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preceding year, left eye worse than right, and worse in the morning. She had been previously diagnosed with an early-onset form of Fuchs dystrophy, identified as the p.(Leu450Trp) mutation in COL8A2. At the time of presentation, the best corrected visual acuity (BCVA) was 20/50 OU. Slit-lamp examination revealed moderate guttate with microcystic edema extending to the peripheral cornea, and mild nuclear sclerosis in both eyes. Central corneal thickness (CCT) was 642 μm and 678 μm in OD and OS, respectively, measured by corneal topography.

The patient first underwent cataract extraction with intraocular lens (IOL) implantation with DMEK in the left eye. Using the Holladay 2 formula, a 24.0D MA50BM IOL (Alcon Laboratories, Inc, Fort Worth, TX, USA) was selected, predicting a spherical equivalent of -1.0 D. The epithelium was removed to improve visualization, and Descemet membrane was scored and stripped without complication. The graft was centered and attached throughout the follow-up period. Supplemental Table 1 demonstrates post-operative data and endothelial cell density at follow-up visits.

After best-corrected visual acuity had improved to 20/20 at one week, the patient elected to proceed with phacoemulsification and DMEK in the right eye. Based on the post-operative refraction in OS, which suggested a hyperopic shift from the expected refractive outcome, the aim for the right eye was adjusted to -1.4 D using the Holladay 2 formula and a 25.0D MA50BM IOL.

In the right eye, the procedure was uneventful and the graft well-centered. Pathology demonstrated a thickened Descemet membrane with buried guttae (Supplemental Fig. 1), with mean thickness of 28 μm. One week after surgery, the graft was attached, with inferior bullae and trace edema noted, greatest temporally.

Notably, over the following year, both eyes experienced significant refractive shifts (Supplemental Table 1). In the left eye, a rapid decrease in central corneal thickness resulted in a hyperopic shift at one month, which then evolved to a myopic shift as the peripheral cornea began to clear. In the right eye, a significant myopic shift occurred between postoperative months 3 and 6 as the peripheral cornea also began to clear. At the last follow-up visit three years after surgery, both the central and peripheral corneas remained clear.

2.2. Case 2

A 56-year-old man, the brother of the patient in Case 1, presented with decreased vision and a known p.(Leu450Trp) mutation in COL8A2. BCVA was 20/70 and 20/50 in the right and left eyes, respectively. Slit-lamp examination revealed diffuse corneal edema, thickening and anterior haze OU, and mild nuclear sclerosis OU. The remainder of the slit-lamp examination, including retinal evaluation, was unremarkable. Central corneal thickness was 876 μm and 679 μm in OD and OS, respectively. The decision was made to proceed with DMEK and cataract surgery concurrently, starting with the right eye.

Expecting a hyperopic shift after surgery, a 22.0 D, three-piece Alcon MA50BM IOL (Alcon Laboratories, Inc, Fort Worth, TX, USA) was

selected, predicting a spherical equivalent of -1.3D postoperatively using the Holladay 2 formula. Due to diffuse edema and a limited view, the epithelium was debrided and Descemet membrane was notably thickened, coming out as a sheet with greater tensile strength than was expected from Descemet membrane in common variants of late-onset Fuchs dystrophy. Pathology revealed markedly thickened Descemet membrane with buried guttae (Supplemental Fig. 2) and thickness of 120 μm, consistent with this long-standing early-onset corneal endothelial dystrophy.

The graft rapidly cleared during the follow-up period (Fig. 1). At one month, Scheimpflug imaging revealed a 2.6D increase in anterior keratometry, and a spherical equivalent of -3.5D. By six months, the cornea returned to within 0.4D of its original power and spherical equivalent of -1.25D, approximating the refractive goal. Supplemental Table 2 shows post-operative data at each follow-up visit.

The patient subsequently underwent DMEK with concurrent cataract surgery in the left eye, aiming for -1.39D with a 21.5D Alcon MA50BM IOL. This was completed without complication (Video 1; Supplemental Digital Content) and the corneal haze secondary to chronic edema increasingly cleared over time. The final spherical equivalent of -1D approximated the refractive target.

Supplementary video related to this article can be found at <https://doi.org/10.1016/j.ajoc.2022.101544>.

Due to a change in the computer system, data regarding peripheral thickness was only available for one eye, the right eye of Patient 2 (Supplemental Table 3). These data confirm that while central edema rapidly decreased in the first month, peripheral edema at 8mm continued to gradually decrease over a 6-month period.

3. Discussion

In this case series, we describe the postoperative course in four eyes from two patients who underwent DMEK for COL8A2-associated corneal dystrophy, the first description of outcomes of DMEK for eyes affected by the p.(Leu450Trp) COL8A2 mutation.

In classic, late-onset Fuchs dystrophy, anterior corneal changes are associated with disease severity, with minimal impact early in the disease course.⁵ In the p.(Leu450Trp) mutation in COL8A2, patients typically begin to experience corneal edema around 5 years of age, which often leads to epithelial and anterior stromal disease at the time of clinical presentation. Therefore, regardless of whether the morphology of the bullae and pattern of edema varies between patients harboring this specific mutation or more common variants, the earlier onset means there is a higher probability of presenting with bullae at any given age in patients with this mutation.²

In addition, the data here demonstrate significant refractive shifts over the first several months following surgery, suggesting that surgeons should not completely rely on keratometry readings for post-operative management. While our sample size limits our ability to predict the exact amount of change in post-operative refraction, patients with this

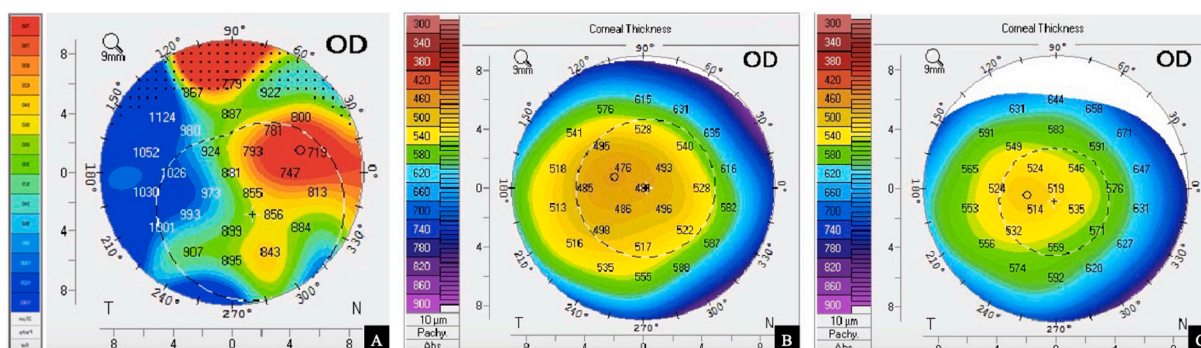


Fig. 1. Pachymetry of the right eye of Patient 2 pre-operatively (A), 3 months post-operatively (B), and 6 months post-operatively (C).

condition undergoing DMEK should still be counseled that refraction may not be stable within the first several months postoperatively. The surgical considerations for patients with *COL8A2*-associated corneal dystrophy are similar to those with advanced Fuchs endothelial dystrophy and pseudophakic bullous keratopathy. However, given the earlier presentation of *COL8A2*-associated corneal dystrophy, phakic DMEK may be considered to retain accommodation.

Although the p.(Leu450Trp) *COL8A2* mutation results in corneal swelling, some genetic variants in *COL8A2* have been previously associated with thinner corneas at baseline.⁷ Performing DMEK, without a net addition of stroma, allows for the cornea to resume its more natural state. Of the four eyes, the minimum thickness reached 482, 479, 479 and 533 μm . These results suggest the possibility that the p.(Leu450Trp) *COL8A2* mutation is also associated with corneal thinning.

Drawing on these experiences, several strategies became apparent for performing DMEK in corneas affected by the p.(Leu450Trp) *COL8A2* mutation. First, given that edema was quite severe, we found it helpful to remove the epithelium at the beginning of the case to improve visualization. In such cases, we found that the epithelium was hypertrophied and even vascularized. Second, since Descemet membrane is quite thick,⁸ we found it helpful to err on the side of a larger Descemetorhexis. Third, in our grafts we use peripheral “I–III” orientation markings at the edge of the graft, to indicate appropriate orientation when aligned in a clockwise fashion. We found this helpful postoperatively for viewing the edge of the graft even in the periphery where edema took time to resolve.

Rapid improvement in visual acuity is a characteristic of DMEK and approximately half of patients undergoing this surgery typically achieve $\geq 20/20$ visual acuity by one month,⁹ although improvement time is typically dependent on baseline patient characteristics including disease severity. In this series, eyes experienced diffuse corneal haze from chronic edema over decades, resulting in rapid resolution of central edema after surgery but taking approximately one year to reach 20/20 BCVA. Given that patients with this mutation may experience edema early in life but present at an older age for surgery, affected individuals undergoing DMEK with this mutation may benefit from discussion that vision may improve for at least one year after surgery. \

4. Conclusions

In conclusion, in two patients with the p.(Leu450Trp) mutation in *COL8A2* who underwent DMEK, we observed refractive and anterior keratometric changes postoperatively with rapid resolution of central corneal edema, and more gradual resolution of both corneal haze and peripheral edema. Patients can have hope that, despite haze in the cornea from swelling for many years, the cornea maintains potential for clarity and an excellent visual outcome.

Patient consent

A draft of the report was shared with the patient and family and written informed consent was provided for the contents of the case report.

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Authorship

All authors attest that they meet the current ICMJE criteria for

Authorship.

Ethics approval

Ethics approval was waived by the Institutional Research Board at the Johns Hopkins University School of Medicine for this case as it represents a retrospective case report.

CRedit authorship contribution statement

Daliya Dzhaber: Conceptualization, Formal analysis, Investigation, Roles, Writing – original draft. **Michael J. Fliotics:** Data curation, Project administration, Writing – review & editing. **Mya Abousy:** Validation, Formal analysis, Writing – review & editing, Conceptualization, Formal analysis, Investigation, Roles, Writing – original draft. **Sepideh Siadati:** Methodology, Resources, Validation, Writing – review & editing. **Charles G. Eberhart:** Methodology, Resources, Validation, Writing – review & editing. **John D. Gottsch:** Conceptualization, Writing – review & editing. **Allen O. Eghrari:** Supervision, Conceptualization, Formal analysis, Investigation, Roles, Writing – original draft.

Declaration of competing interest

The authors have no conflicts of interest to report.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ajoc.2022.101544>.

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