Are Descemet Membrane Ruptures the Root Cause of Corneal Hydrops in Keratoconic Eyes?

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• PURPOSE: **To challenge the current consensus on the mechanism causing corneal hydrops in eyes with keratoconus (KC).**
• DESIGN: **Retrospective, interventional case series.**
• METHODS: **Sixteen eyes of 10 patients with comorbid KC and Fuchs endothelial corneal dystrophy (FECD) underwent uncomplicated Descemet membrane endothelial keratoplasty (DMEK), and 5 eyes of 5 patients with KC alone underwent Bowman layer (BL) transplantation complicated by inadvertent perforation of the posterior corneal stroma and Descemet membrane (DM). The presence or absence of hydrops was assessed by intra- and postoperative optical coherence tomography and by slit-lamp biomicroscopy.**
• RESULTS: **None of the 16 DMEK eyes manifested a hydrops at any time during or after surgery. By contrast, all 5 eyes undergoing BL transplantation complicated by posterior corneal perforation demonstrated a corneal hydrops, evident both intra- and postoperatively.**
• CONCLUSIONS: **In eyes with KC, even the complete removal of DM did not produce a hydrops, whereas a combined defect in DM and the posterior corneal stroma seemed to consistently elicit a typical corneal hydrops. (Am J Ophthalmol 2019;205:147–152. © 2019 Elsevier Inc. All rights reserved.)**

IN KERATOCONIC EYES, CORNEAL HYDROPS IS CHARACterized by the explosive accumulation of intrastromal fluid-filled clefts.[1] The conventional theory provides that these clefts are the result of stretching and then rupture of the Descemet membrane (DM), resulting in acute, severe edema.

This pathogenic theory is widely held, first propounded in 1906 by Terrien in Pierse and Eustace.[2] It is also corroborated by volumes of pathology specimens, which inevitably show evidence of DM disruption in corneas with prior hydrops.[3,4] For that reason, a direct causal connection between DM rupture and hydrops has been assumed, and so far, no clinical observation has suggested otherwise.

Surprisingly, however, with the introduction of various lamellar keratoplasty techniques in the past decade as well as imaging techniques such as anterior segment optical coherence tomography (AS-OCT) and Scheimpflug imaging, clinical observation may now question a causal link between a DM rupture and development of a hydrops in keratoconus (KC). In fact, 2 specific surgical maneuvers may be regarded as a test to disprove the relationship and/or to suggest a different pathological mechanism.

If DM rupture in KC would cause hydrops, the performance of a descemetorhexis during an endothelial keratoplasty procedure[5,6] in eyes with a KC and co-existing endothelial dysfunction would be expected to consistently elicit severe corneal edema. The same holds true for perforations in Bowman layer (BL) transplantation performed in KC eyes,[7-9] as it creates a break from a posterior stromal level into the anterior chamber of the eye.

The present study compared various disruptions of the posterior corneal layers, for example, selective removal of DM in Descemet membrane endothelial keratoplasty (DMEK) in KC eyes and perforations in BL transplantation, to re-evaluate any causal relationship with the development of hydrops in KC.

SUBJECTS AND METHODS

THIS RETROSPECTIVE STUDY ENROLLED PATIENTS FROM 2 tertiary referral centers: Parker Cornea (Center 1) and Melles Cornea Clinic Rotterdam (Center 2). Sixteen eyes (14 phakic) of 10 patients (8 male; mean age, 54 ± 9 years; range, 37-67 years of age) with a history of comorbid KC and Fuchs endothelial corneal dystrophy (FECD) underwent DMEK (Table). Five additional eyes (5 phakic) of 5 patients (3 male; mean age, 39 ± 13 years of age; range, 20-57 years of age) underwent BL transplantation and experienced an inadvertent posterior perforation during the stromal dissection component of the operation (Table). All patients had signed an informed consent for research participation prior to surgery, and

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TABLE. Overview Baseline Characteristics

	Patient Characteristics							Preoperative Corneal Measurements			
Center	Case No.	Age (y)/Sex	Race	Eye	Surgical Procedure	Indication for Surgery	Lens Status	Kmax (D)	TPT (μm)	Intra- or Postoperative Corneal Hydrops	Remarks
1	1a	64/M	C	OS	DMEK*	FECD	Phakic	55.5	523	No	
1	1b	67/M	C	OD	DMEK*	FECD	Phakic	56.4	577	No	
1	2a	42/M	AA	OS	DMEK	FECD	Pseudophakic	60.8	450	No	Near-total detachment on first postoperative day; reoperated with DSAEK at 3 postoperative wks
1	2b	43/M	AA	OD	DMEK*	FECD	Phakic	45.3	506	No	
1	3a	47/M	C	OD	DMEK	FECD	Phakic	47.1	522	No	Partial graft detachment; rebubbled successfully at 4 postoperative d
1	3b	48/M	C	OS	DMEK	FECD	Phakic	46.1	491	No	
1	4a	64/M	C	OD	DMEK*	FECD	Phakic	49.9	464	No	
1	4b	65/M	C	OS	DMEK*	FECD	Phakic	48.4	455	No	
1	5	54/F	AA	OD	DMEK*	FECD	Phakic	44.6	481	No	
1	6	57/F	AA	OD	DMEK	FECD	Pseudophakic	63.0	514	No	Near-total detachment on first postoperative d; reoperated with DSAEK at 1 postoperative wk
1	7a	57/M	C	OD	DMEK	FECD	Phakic	50.4	679	No	
1	7b	57/M	C	OS	DMEK	FECD	Phakic	50.4	673	No	
1	8	37/M	C	OS	DMEK	FECD	Phakic	66.8	606	No	
1	9	58/M	AA	OS	DMEK	FECD	Phakic	77.7	233	No	Near-total graft detachment on first postoperative day; reoperated with PK at 1 postoperative week
1	10a	55/M	C	OS	DMEK*	FECD	Phakic	44.5	600	No	
1	10b	55/M	C	OD	DMEK*	FECD	Phakic	55.2	614	No	
1	11	38/F	C	OS	BLT	KC	Phakic	70.6	391	Yes	Perforation during stromal dissection at the apex of the cone; operation was aborted
1	12	57/M	C	OS	BLT	KC	Phakic	70.9	289	Yes	Perforation during stromal dissection at the apex of the cone; the operation was aborted
2	13	43/M	AA	OS	BLT	KC	Phakic	79.1	202	Yes	Perforation during stromal dissection at the apex of the cone; the graft was implanted successfully
2	14	35/M	C	OS	BLT	KC	Phakic	108.4	253	Yes	Perforation during stromal dissection at the apex of cone; the graft was implanted successfully
2	15	20/F	AA	OD	BLT	KC	Phakic	78.6	317	Yes	Perforation occurred during stromal dissection at the apex of the cone; the operation was aborted

AA = African American; BLT = Bowman layer transplantation, C = caucasian; D = diopters; DMEK = Descemet membrane endothelial keratoplasty; *DMEK = DMEK combined with phacoemulsification and IOL implantation; DSAEK = Descemet stripping automated endothelial keratoplasty; F = female; FECD = Fuchs endothelial corneal dystrophy; IOL = intraocular lens; Kmax = maximum keratometry; KC = keratoconus, eyes from the same patient are indicated with a or b; M = male; OD = oculus dexter; OS = oculus sinister; PK = penetrating keratoplasty; TPT = thinnest point corneal thickness.

the study was conducted in accordance with the tenets of the Declaration of Helsinki.

• **DONOR TISSUE:** All DMEK grafts were prepared according to local protocol. From whole globes obtained less than 36 hours postmortem, corneoscleral buttons were excised and stored in Optisol-GS corneal storage medium (Bausch & Lomb, Inc, Rochester, New York, USA) until the time of preparation, whereupon they were removed from storage, rinsed with balanced salt solution (Bausch & Lomb), and stained with a 0.06% Trypan blue solution (VisionBlue, DORC International, Zuidland, The Netherlands). The peripheral DM was loosened circumferentially and stripped toward the center, preserving a small central area of attachment with the posterior stroma. The entire corneoscleral button (with the graft attached) was then returned to Optisol-GS storage medium until the time of surgery.

BL grafts were likewise prepared according to standard protocol: a corneoscleral rim was mounted on an artificial anterior chamber, debrided of epithelium, and stained using a 0.06% Trypan blue solution drip. BL was incised 360 degrees around, just inside the limbus, using a 30-guage needle. Nontoothed forceps were then used to delicately peel the BL away from the underlying anterior stroma, after which the graft was submerged in 70% ethanol for 30 seconds and stored again until the time of transplantation.

• **SURGERY:** All DMEK surgeries were performed at Center 1 and, in 8 of the 16 eyes (50%), was combined with phacoemulsification and intraocular lens implantation. After the creation of a paracentesis, the anterior chamber was filled with air, and the host DM was stripped using a reversed Sinsky hook (Dutch Ophthalmic Research Center [DORC], International, Zuidland, the Netherlands). After the donor DM was re-stained with Trypan blue, the graft was delivered into the eye using a dedicated glass injector (DORC International) through a 3.0-mm clear corneal wound. Unfolding proceeded by indirect manipulations, that is, corneal surface taps and intracameral bursts of balanced salt solution. Intraoperative AS-OCT (Callisto; Carl Zeiss Meditec, Inc, Dublin, California, USA) was used to confirm the orientation of the graft and to inspect the recipient posterior stroma for irregularities. Once the graft was properly positioned, a the anterior chamber was filled with air and maintained for 60 minutes, after which the size of the air-bubble was reduced to 50%, and the operation concluded.

BL transplantations[9] were performed at both Center 1 and Center 2. A superior conjunctival peritomy was made, followed by a 5-mm long, partial-thickness scleral incision 1-2 mm posterior to the limbus that was tunneled up into the clear cornea with a crescent blade. The anterior chamber was filled with air through paracentesis. Then, a set of curved spatulas (Melles spatula set; DORC International) was used to dissect a mid-stromal pocket (aiming at 50% stromal depth) from limbus-to-limbus, 360 degrees around within the recipient cornea, into which the donor BL graft was placed. At Center 1, mid-stromal dissection was performed under intraoperative AS-OCT guidance, whereas this technology was not available at Center 2. In case of inadvertent posterior perforation, the operation was continued, and BL graft implantation proceeded unless further stromal dissection became impossible, in which case the operation was aborted.

All DMEK and BL transplantation patients at both centers were evaluated before and 1 day after surgery and then at 1 week and 1 month after surgery using rotating Scheimpflug corneal tomography (Pentacam HR; Oculus, Wetzlar, Germany), slit-lamp biomicroscopy, and AS-OCT (Visante; Carl Zeiss Meditec at Center 1; or Heidelberg Engineering GmbH, Heidelberg, Germany, at Center 2).

RESULTS

• **DESCEMET MEMBRANE ENDOTHELIAL KERATOPLASTY:** All DMEK surgeries were uncomplicated. During surgery, following descemetorhexis but before graft implantation, no eye demonstrated corneal hydrops, either by direct inspection or by evaluation with intraoperative AS-OCT (Figure 1).

According to postoperative examination using AS-OCT, on the first postoperative day and at all subsequent follow-up examinations, 12 of 16 DMEK grafts (75%) showed complete attachment to the recipient posterior stroma (Table). One of the 16 eyes (6%) manifested a partial graft detachment, which was successfully rebubbled 4 days after the initial operation. Three additional grafts (19%) demonstrated near-complete detachments on the first postoperative day; these 3 eyes subsequently underwent repeated keratoplasty, performed between 1 and 3 weeks after the initial DMEK operation (Table). Postoperatively, corneal hydrops was not detected in any of the 16 eyes.

• **BL TRANSPLANTATION WITH PERFORATION:** In 3 of the 5 BL transplantations complicated by posterior perforation (60%), further stromal dissection proved impossible, and the operation was aborted, whereas in 2 of the 5 eyes (40%) the operation could be completed (Table).

In all 5 cases, a corneal hydrops was immediately apparent following perforation by direct inspection and was confirmed by using intraoperative AS-OCT at Center 1 (Figure 1). Postoperative AS-OCT performed the day

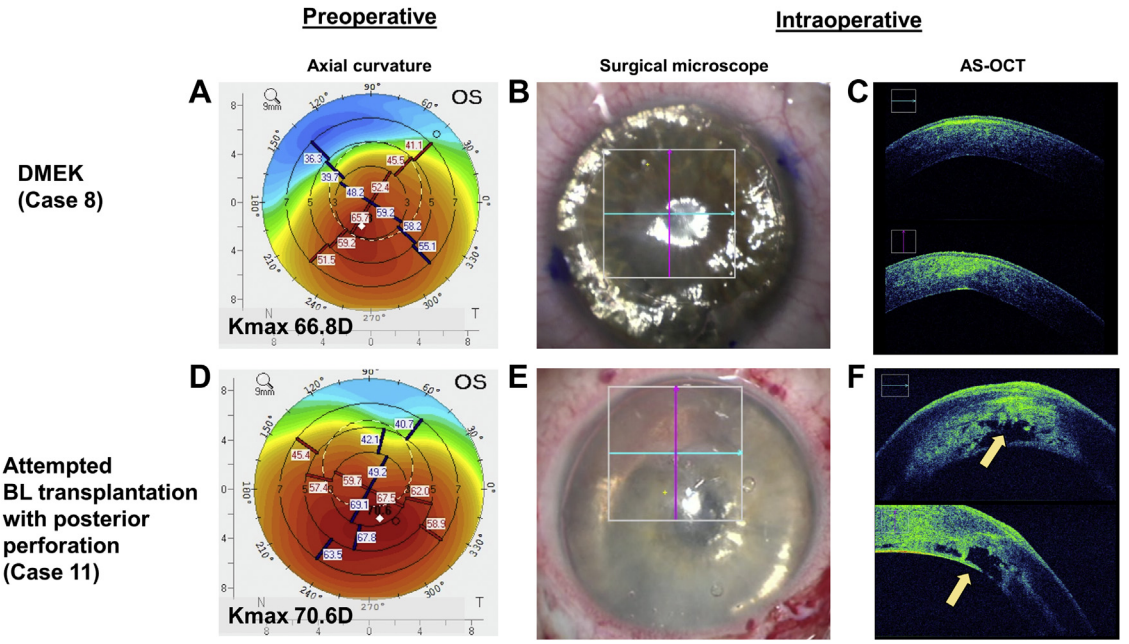

FIGURE 1. Preoperative axial curvature measurements and intraoperative anterior segment optical coherence tomography images of a patient with both advanced keratoconus and Fuchs endothelial corneal dystrophy (Case 8) and a patient with keratoconus alone (Case 11). Preoperative axial curvature measurements obtained from a patient with both advanced keratoconus (KC) and Fuchs endothelial corneal dystrophy (A). During subsequent Descemet membrane endothelial keratoplasty (DMEK), after descemetorhexis but before graft implantation, no corneal hydrops is grossly observable through the operating microscope (B), nor is any evident by intraoperative anterior segment optical coherence tomography (AS-OCT) (C). By contrast, in another eye with advanced KC alone (D), during an attempt to transplant Bowman layer (BL), an inadvertent posterior perforation during the stromal dissection portion of the operation immediately results in corneal hydrops (arrows in F), grossly observable through the operating microscope (E) and with intraoperative AS-OCT (F). Kmax = maximum keratometry.

after surgery likewise demonstrated a corneal hydrops in all 5 eyes at both centers (Figure 2).

DISCUSSION

THE AUTHORS' OBSERVATIONS IN KERATOCONIC EYES requiring DMEK and those experiencing corneal perforation during intrastromal BL transplantation question the current consensus that corneal hydrops in keratoconic eyes arises from an isolated break in the DM.

In this series of patients with combined FECD and KC, the (nearly) entire recipient DM was scored and then removed. In 25% of cases, this was followed by a prolonged period of partial or (nearly) complete endothelial graft detachment. Nevertheless, none of the study eyes (consisting of cases of mild, moderate, advanced, and very advanced KC) developed corneal hydrops. By contrast, in keratoconic eyes undergoing BL transplantation, inadvertent perforation through the posterior stroma and DM during the manual dissection portion of the operation invariably produced a classic corneal hydrops, immediately evident by intraoperative AS-OCT and persistently observable on postoperative clinical examination and imaging studies (Figure 2).

These dual observations may indicate that a defect at the level of DM is not sufficient to elicit an acute corneal hydrops, unless also accompanied by a defect in the posterior corneal stroma. In fact, these findings may suggest that a rupture of the most posterior stroma is decisive for corneal hydrops to occur (Figure 3). These posterior-most stromal layers have been the recent subject of attention and controversy (the so-called Dua layer), in part because of the special behavior and mechanical properties they are believed to possess, including high tensile strength, impermeability to air, and a distinctive collagen makeup featuring a greater amount of type VI collagen and longer spacing fibrils.[10,11] Abnormalities of these layers have previously been identified in a number of corneal conditions, including corneal hydrops.[12] In 2015, Chérif and associates[13] demonstrated that compression sutures placed in the deep posterior stroma may be an effective treatment for corneal hydrops and theorized that posterior stromal breaks were the root cause of the condition.

One limitation of the present study is the difference in keratoconic severity between the 2 groups of operated

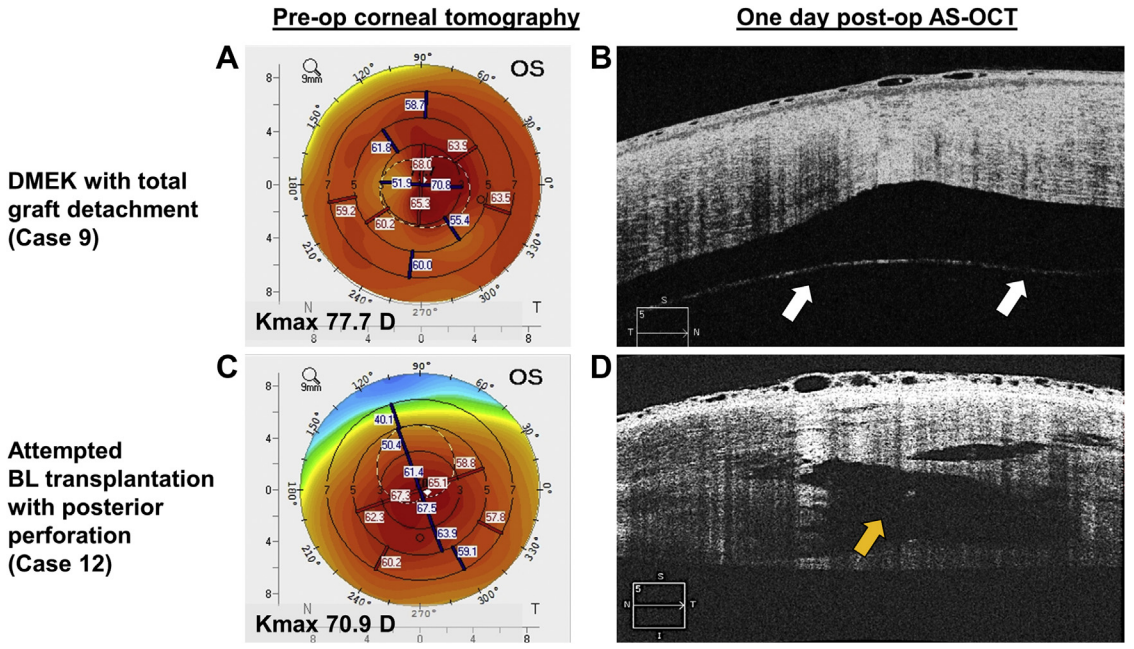

FIGURE 2. Clinical images of a patient with both advanced keratoconus and Fuchs endothelial corneal dystrophy (Case 9) and a patient with keratoconus (KC) alone (Case 12). An eye with advanced KC and Fuchs endothelial corneal dystrophy underwent uncomplicated Descemet membrane endothelial keratoplasty (DMEK) (A). Although, 1 day after surgery, anterior segment optical coherence tomography (AS-OCT) images demonstrated near total graft detachment (white arrows), no corneal hydrops was seen (B). By contrast, in another eye with advanced KC alone (C), 1 day after surgery, AS-OCT images following Bowman layer transplantation with inadvertent posterior perforation demonstrate classic corneal hydrops with intrastromal fluid clefts (orange arrow) (D). Kmax = maximum keratometry.

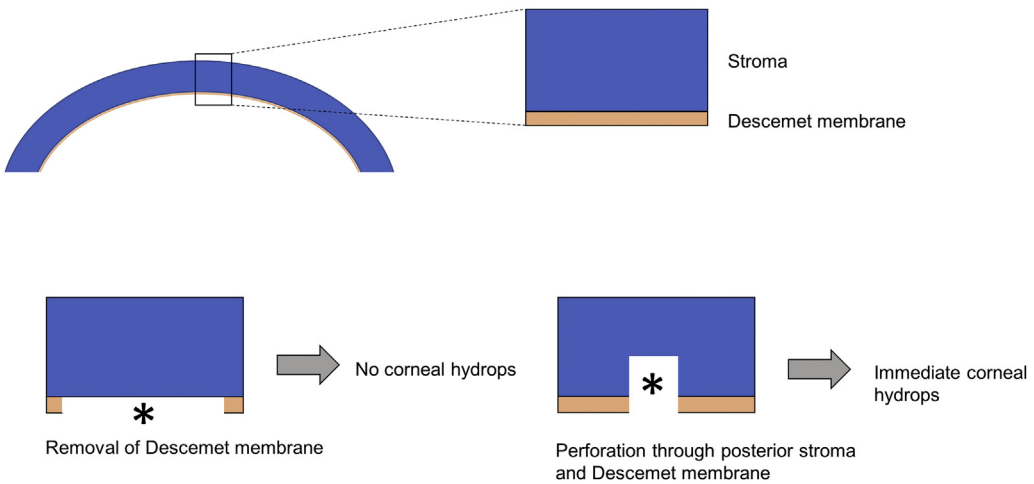

FIGURE 3. Theoretical alternate pathological mechanism for the generation of corneal hydrops.

eyes, namely, the eyes receiving BL transplantation tended to have more advanced KC than those receiving DMEK. Nevertheless, a significant fraction of the eyes undergoing DMEK were classified as "advanced" or "very advanced" KC, and it may be significant that none developed a classic corneal hydrops, despite undergoing DM removal and, in several instances, persistent postoperative DM detachment.

Further study involving a larger series of eyes and, potentially, including other forms of lamellar keratoplasty including deep anterior lamellar keratoplasty and deep lamellar endothelial keratoplasty may be more instructive.

Meanwhile, the results of this study may agree with those reports in that the posterior corneal stroma is somehow involved in the development of a corneal hydrops and, if so, prevention and or treatment may potentially be sought at this corneal level rather than at the level of DM.

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REFERENCES

1. Feder RS, Wilhelmus KR, Vold SD, O'Grady RB. Intrastromal clefts in keratoconus patients with hydrops. *Am J Ophthalmol* 1998;126(1):9–16.
2. Pierse D, Eustace P. Acute keratoconus in Mongols. *Br J Ophthalmol* 1971;55(1):50–54.
3. Stone DL, Kenyon KR, Stark WJ. Ultrastructure of keratoconus with healed hydrops. *Am J Ophthalmol* 1976;82(3):450–458.
4. Chi HH, Katzin HM, Teng CC. Histopathology of keratoconus. *Am J Ophthalmol* 1956;42(6):847–860.
5. Gupta R, Kinderyte R, Jacobs DS, Jurkunas UV. Elimination of anterior corneal steepening with Descemet membrane endothelial keratoplasty in a patient with Fuchs dystrophy and keratoconus: Implications for IOL calculation. *Cornea* 2017;36(10):1260–1262.
6. Cooper E, Parker J, Parker J, Melles GRJ. Descemet membrane endothelial keratoplasty in an eye with Fuchs endothelial dystrophy and keratoconus. *Ophthalmol @ Point Care* 2017;1(1):e8–e10. https://doi.org/10.5301/oapoc.0000002.
7. van Dijk K, Parker JS, Baydoun L, et al. Bowman layer transplantation: 5-year results. *Graefes Arch Clin Exp Ophthalmol* 2018;256(6):1151–1158.
8. van Dijk K, Liarakos VS, Parker J, et al. Bowman layer transplantation to reduce and stabilize progressive, advanced keratoconus. *Ophthalmology* 2015;122(5):909–917.
9. van Dijk K, Parker J, Tong CM, et al. Midstromal isolated Bowman layer graft for reduction of advanced keratoconus: a technique to postpone penetrating or deep anterior lamellar keratoplasty. *JAMA Ophthalmol* 2014 1;132(4):495–501.
10. Dua HS, Faraj LA, Said DG, Gray T, Lowe J. Human corneal anatomy redefined: a novel pre Descemet's layer (Dua's layer). *Ophthalmology* 2013;120(9):1778–1785.
11. Dua HS, Mastropasqua L, Faraj L, et al. Big bubble deep anterior lamellar keratoplasty: the collagen layer in the wall of the big bubble is unique. *Acta Ophthalmol* 2015;93(5):427–430.
12. Dua HS, Said DG. Clinical evidence of the pre-Descemets layer (Dua's layer) in corneal pathology. *Eye (Lond)* 2016;30(8):1144–1145.
13. Yahia Chérif H, Gueudry J, Afriat M, et al. Efficacy and safety of pre-Descemet's membrane sutures for the management of acute corneal hydrops in keratoconus. *Br J Ophthalmol* 2015;99(6):773–777.