Corneal Hydration Control in Fuchs' Endothelial Corneal Dystrophy

Katrin Wacker, Jay W. McLaren, Katrina M. Kane, Keith H. Baratz, and Sanjay V. Patel

Department of Ophthalmology, Mayo Clinic, Rochester, Minnesota, United States

Correspondence: Sanjay V. Patel, Department of Ophthalmology, 200 First Street SW, Rochester, MN 55905, USA; patel.sanjay@mayo.edu.

Submitted: June 27, 2016
Accepted: August 15, 2016

Citation: Wacker K, McLaren JW, Kane KM, Baratz KH, Patel SV. Corneal hydration control in Fuchs' endothelial corneal dystrophy. *Invest Ophthalmol Vis Sci*. 2016;57:5060–5065. DOI:10.1167/iovs.16-20205

Purpose. To assess corneal hydration control across a range of severity of Fuchs' endothelial corneal dystrophy (FECD) by measuring the percent recovery per hour (PRPH) of central corneal thickness after swelling the cornea and to determine its association with corneal morphologic parameters.

Methods. Twenty-three corneas of 23 phakic FECD patients and 8 corneas of 8 healthy control participants devoid of guttae were graded (modified Krachmer scale). Effective endothelial cell density (ECD_e) was determined from the area of guttae and local cell density in confocal microscopy images. Steady-state corneal thickness (CT_{ss}) and standardized central corneal backscatter were derived from Scheimpflug images. Corneal swelling was induced by wearing a low-oxygen transmissible contact lens for 2 hours in the morning. De-swelling was measured over 5 hours after lens removal or until corneal thickness returned to CT_{ss}. Percent recovery per hour was $100 \times (1 - e^{-k})$, where k was determined from $CT(t) = (de^{-kt}) + CT_{ss}$, and where d was the initial change from CT_{ss}.

Results. After contact lens wear, corneas swelled by 9% (95% CI 9–10). Percent recovery per hour was 49%/h (95% CI 41–57) in controls and 37%/h in advanced FECD (95% CI 29–43, $P = 0.028$). Low PRPH was associated with disease severity, low ECD_e, and increased anterior and posterior corneal backscatter. Anterior backscatter was associated with PRPH in a multivariable model ($R^2 = 0.44$).

Conclusions. Corneal hydration control is impaired in advanced FECD and is inversely related to anterior corneal backscatter. Anterior corneal backscatter might serve as an indicator of impaired endothelium in FECD.

Keywords: Fuchs' dystrophy, corneal endothelial cells, corneal edema

Fuchs' endothelial corneal dystrophy (FECD) is characterized by the presence of endothelial guttae and corneal edema from progressive endothelial dysfunction.[1] Fuchs' endothelial corneal dystrophy has traditionally been considered to have nonedematous and edematous stages,[2] and this is still reflected in current clinical grading scales that assess progressive morphologic changes in guttae and the presence of clinically detectable edema only at the most advanced grade.[3,4] Nevertheless, studies of large cohorts of patients with FECD disclose that corneas are thicker than normal early in the course of the disease,[5,6] presumably from subclinical edema, which suggests that corneal endothelial function, whether pump or barrier or both, is compromised early in the course of the disease. This chronic state of edema may contribute to early optical and ultrastructural changes in FECD.[7,8]

Corneal hydration control can be assessed by measuring the percent recovery per hour (PRPH) of corneal thickness after inducing corneal swelling, and barrier function of the endothelium to small molecules can be assessed by fluorophotometry.[9–12] Hypoxia causes corneal lactate accumulation, which produces an osmotic load leading to swelling; removal of lactate is therefore inherent to endothelial pump function and the PRPH measurement.[13] Assuming an intact epithelium, PRPH may serve as a valid measure of overall endothelial function.[11]

Percent recovery per hour has been previously measured in FECD or after endothelial keratoplasty,[14–16] but disease severity was not characterized well by using recognized clinical grading systems, preventing a clear understanding of changes in hydration control with severity of the disease.

In this study, we examined corneal hydration control expressed as PRPH after purposefully swelling the cornea across a range of severity of FECD and in normal corneas. Because this direct measurement of overall endothelial function is time-consuming and not practical in clinical settings, we also measured morphologic parameters of the same corneas at steady-state to assess their association with corneal hydration control. A simple noninvasive and objective measure of the cornea that reflects endothelial function would be ideal in clinical practice to evaluate the functional severity of the disease.

Methods

Participants

Participants of either sex and any race were recruited from the cornea service at Mayo Clinic (Rochester, MN, USA). All participants had FECD or were healthy volunteers older than 50 years. Exclusion criteria were ocular pathology except FECD (in the FECD group only) or cataract, any previous ocular surgery, current contact lens wear, administration of systemic or topical medications known to affect the cornea, or systemic

Investigative Ophthalmology & Visual Science

Table. Steady-State Characteristics of FECD and Normal Corneas

	Normal	FECD		
		Mild	Moderate	Advanced
FECD grade	0	1–2	3–4	5–6
Eyes	8	8	4	11
Median age, y (range)	60 (54–83)	68 (55–86)	58 (44–62)	67 (60–89)
Female (%)	5 (63)	5 (63)	3 (75)	6 (55)
ECD_e, cells/mm^2	2339 ± 258	1808 ± 439	1023 ± 764†	320 ± 267†
CT_{ss}, μm	541 ± 31	540 ± 23	566 ± 15	583 ± 41*
Induced swelling, μm	50 ± 11	48 ± 12	58 ± 14	57 ± 12
Anterior backscatter, SU	1309 ± 64	1374 ± 49	1453 ± 110	1599 ± 185†
Posterior backscatter, SU	727 ± 227	834 ± 119	742 ± 131	981 ± 150*

Mean ± SD of ECD_e, CT_{ss}, and corneal backscatter measured in SU. Comparisons between FECD and normal were adjusted for age and multiple comparisons with the Bonferroni method.

* $P < 0.05$.

† $P < 0.001$.

diseases that could affect the cornea including diabetes. This study was reviewed and approved by the Institutional Review Board at Mayo Clinic; the research followed the tenets of the Declaration of Helsinki. Informed consent was obtained from the subjects after explanation of the nature and possible consequences of the study.

Clinical Grading and Corneal Imaging at Steady-State

Enrollment visits were scheduled on an afternoon when corneas were assumed to be at steady-state. Fuchs' endothelial corneal dystrophy was graded clinically by a trained observer (KW, KHB, or SVP) based on the area and confluence of guttae, and the presence of edema by using slit-lamp biomicroscopy.[3,4] Corneas without guttae were categorized as normal (grade 0). Corneas with 1 to 12 or 12 or more nonconfluent central guttae (grades 1 and 2) were considered to have mild FECD; corneas with confluent guttae of 1- to 2-mm and 2- to 5-mm diameter (grades 3 and 4) were considered to have moderate FECD; and corneas with more than 5-mm diameter of confluent guttae or any visible edema (grades 5 and 6) were considered to have advanced FECD.[17] The epithelium was intact and without bullae in all participants.

Effective endothelial cell density (ECD_e) was determined by using confocal microscopy (Confoscan 4; Nidek Technologies, Freemont, CA, USA) with a widefield (×20) noncontact objective. Images of the endothelium were analyzed by a standardized image-processing method that determined the area of guttae and local endothelial cell density.[18] Central corneal thickness was determined from tomographic images acquired by using a rotating Scheimpflug camera (Pentacam HR; Oculus, Lynnwood, WA, USA) as described previously.[17]

Central corneal haze (backscatter) in the anterior 120 μm and posterior 60 μm of the cornea was also determined from Scheimpflug images.[7] All corneal backscatter measurements were standardized by adjusting corneal image brightness to that of a fixed scatter source to account for any fluctuations in the intensity of the light source and sensitivity of the detection system over time.[19,20] All Scheimpflug images were checked for data acquisition errors (Pentacam software version 1.20r29). Axial resolution of our instrument is 11.8 μm per pixel (range, 11.5–12.4 μm per pixel); because of the software's surface-fitting algorithm, axial resolution should be better than the resolution of one pixel.[17] Others have reported the precision of central corneal thickness to be within 3 to 7 μm (Schwiegerling J, et al. *IOVS* 2007;48:ARVO E-Abstract 3539).

Inducing Corneal Swelling

Follow-up visits for measurement of corneal hydration control started at approximately 8:00 AM and Scheimpflug images were repeated before any intervention. A low-oxygen transmissible hydrogel contact lens (Polymacon; oxygen permeability, 7.9×10^{-11} cm^2/s mL O_2/mL mm Hg; Westcon Contacts, Duluth, GA, USA) with thickness of 500 μm and diameter of 12 mm was placed on one eye and the eyelid was taped closed. The contact lens base curve was 8.0 mm or 8.2 mm depending on the patient's corneal curvature and clinical assessment of contact lens fit and centration. After 2 hours, the contact lens was removed and Scheimpflug images were immediately acquired. Scheimpflug photography was then repeated every 15 minutes for the next hour and every 30 minutes through 5 hours or until corneal thickness returned to corneal thickness within 5% of the thinner of the measurements at presumed steady-state or immediately before contact lens application (CT_{ss}). Participants were asked not to close their eyes for prolonged periods after contact lens removal. All measurements were taken in the same air-conditioned and humidity-controlled environment.[21]

Statistical Analysis

Descriptive summary statistics were reported as mean ± SD by severity of FECD. Regression models were used to calculate mean differences in steady-state characteristics between FECD groups adjusted for age and multiple comparisons by the Bonferroni method (Table).

Recovery of corneal thickness was expected to follow an exponential curve[10]:

$$\mathrm{CT}(t) = \Big(\mathrm{CT}(0) - \mathrm{CT_{ss}}\Big)e^{-kt} + \mathrm{CT_{ss}} \qquad (1)$$

where CT(t) was corneal thickness at time t after removing the contact lens, CT(0) was corneal thickness immediately after removing the contact lens, and k was a constant. Equation 1 was solved for k by regression for each patient. Percent recovery per hour was determined as follows:

$$\mathrm{PRPH} = 100(1 - e^{-k}) \qquad (2)$$

Time to 95% thickness recovery (T95%) was[15]

$$\mathrm{T95\%} = -\frac{\ln(0.05)}{k} \qquad (3)$$

For a global test of association between PRPH and swelling with severity of FECD in regression models, we used a

likelihood ratio test and a test for trend across FECD groups (grade 0–6). Regression models were used to assess associations between PRPH and CT_{ss}, swelling (difference between central corneal thickness immediately after contact lens removal and the thinner of the two measurements at steady-state or immediately before contact lens application), anterior and posterior steady-state backscatter, and ECD_e with respective 95% confidence intervals (95% CI). Correlations were assessed with Spearman (ρ, ordinal) or Pearson (r, continuous) correlation coefficients. Differences were considered statistically significant if $P < 0.05$ (two-sided tests). Stepwise selection for regression models (removal if $P \geq 0.15$, eligible for addition if $P < 0.1$) was used to identify predictors of PRPH among predefined factors, including CT_{ss}, swelling, anterior and posterior backscatter (all continuous), and ECD_e (binary, >1000 cells/mm^2 vs <1000 cells/mm^2); predicted PRPH values were calculated for significant factors. Careful data and regression diagnostic were conducted to identify possible outliers, leverage, and influence. All statistics were calculated by using Stata version 13.1 (StataCorp, College Station, TX, USA).

Results

Participants

Twenty-three corneas of 23 Caucasian participants with FECD and 8 corneas of 8 Caucasian participants with normal eyes were examined (Table). Age was 67 ± 12 years (mean ± SD) in the FECD group and 63 ± 9 years ($P = 0.4$) in the control group.

Corneal Hydration Control (PRPH)

Mean corneal swelling for the combined groups was 53 μm (95% CI 48–57) or 9.5% (95% CI 8.7–10.3) compared with CT_{ss}; swelling for each group is detailed in the Table. Swelling did not differ between FECD and normal corneas ($P = 0.3$). After solving equation (1) for k, predicted corneal thickness was highly correlated with measured thickness at the same points in time ($r = 0.99$, $P < 0.001$), and those values were not different (mean difference, –0.8 μm; 95% CI –1.7–0.1).

Percent recovery per hour was 49%/h (95% CI 41–57) in normal corneas compared with 45%/h (95% CI 37–53; $P = 0.5$ vs. normal; minimum detectable difference, 13%/h; $\alpha = 0.05$, $\beta = 0.20$) in mild, 37%/h (95% CI 26–49; $P = 0.1$ vs. normal; minimum detectable difference, 16%/h; $\alpha = 0.05$, $\beta = 0.20$), in moderate, and 37%/h (95% CI 29–43; $P = 0.028$ vs. normal) in advanced FECD (Fig. 1). Time to 95% thickness recovery was 4.7 hours (95% CI 2.2–7.1) in normal corneas compared with 5.5 hours (95% CI 3.1–8.0; $P = 0.6$ vs. normal) in mild, 6.9 hours (95% CI 3.5–10.3; $P = 0.3$ vs. normal) in moderate, and 7.8 hours (95% CI 5.7–9.9; $P = 0.053$ vs. normal) in advanced FECD.

Association Between PRPH and Morphologic Parameters

Percent recovery per hour was inversely associated with FECD severity (nonparametric P trend = 0.023; $\rho = -0.42$; Fig. 1) and with ECD_e ($r = 0.37$, $P = 0.039$). Corneas with ECD_e <1000 cells/mm^2 had a lower PRPH (36%/h; 95% CI 30–42) than corneas with ECD_e >1000 cells/mm^2 (46%/h; 95% CI 41–52; $P = 0.011$; Fig. 2). Percent recovery per hour was associated with CT_{ss} ($r = -0.37$; $P = 0.043$). Low PRPH was also associated with higher amounts of induced corneal swelling ($r = -0.54$, $P = 0.002$), and with high central anterior and posterior steady-state backscatter ($r = -0.53$, $P = 0.002$ and $r = -0.49$, $P = 0.005$, respectively).

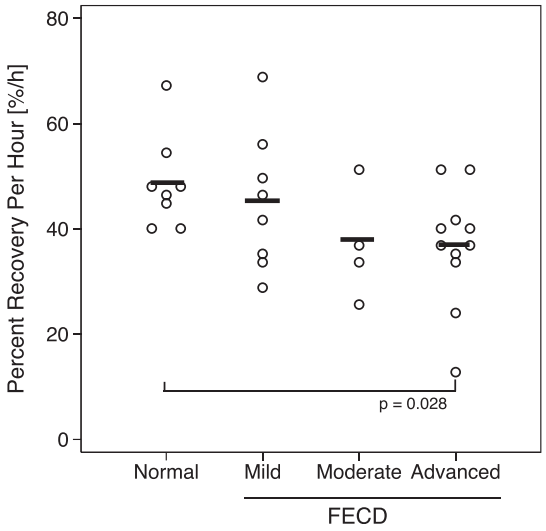

Figure 1. Percent recovery per hour of corneal thickness across a range of severity of FECD and normal corneas. Percent recovery per hour of central corneal thickness was measured by Scheimpflug imaging after purposefully swelling the cornea (FECD, $n = 23$; normal, $n = 8$). Percent recovery per hour was decreased in advanced FECD by 12%/h (95%CI 1–23, $P = 0.028$) compared with normal. *Lines* indicate mean.

In a multivariable analysis, only anterior backscatter ($P = 0.012$) and corneal swelling ($P = 0.009$) were independently associated with PRPH; R^2 for the multivariable model was 0.44. Predicted PRPH values for the identified range of anterior steady-state backscatter are provided in Figure 3 based on corneal swelling of 50 μm.

Discussion

Corneal hydration control and thickness recovery after stress-induced corneal edema are reduced in advanced FECD compared with normal corneas. Anterior corneal backscatter, which is known to be increased early in the course of FECD,[7,8] is associated with overall endothelial function and should be further investigated for its ability to estimate endothelial function in clinical practice.

Ideal control of corneal hydration requires a balance between passive barrier leakage into the cornea and active pump of solute back to the aqueous humor.[9,22] Alterations in corneal hydration can result from pump or barrier dysfunction and are known to adversely affect stromal transparency.[23] In this study, we found that corneal hydration control was impaired in clinically advanced FECD compared with normal and was associated with a delay in recovery of steady-state corneal thickness in FECD; we were unable to detect a significant difference in mild or moderate disease, although there were similar trends toward decreased PRPH. Percent recovery per hour in normal corneas (49%/h, 95% CI 41–57) was similar to that found in a previous study from our laboratory (48%/h; 95% CI 43–53) in normal, young non–contact-lens wearers.[9] Another study found lower PRPH (34%/h in normal corneas and 25%/h in FECD),[15] and these differences might be due to different experimental conditions and FECD severity. Nielsen et al.[16] found a similar amount of swelling in advanced FECD and normal corneas (approximately 44 μm or 7%); PRPH was not determined, but the percentage of swelling was significantly higher in advanced FECD compared with normal.

Investigative Ophthalmology & Visual Science

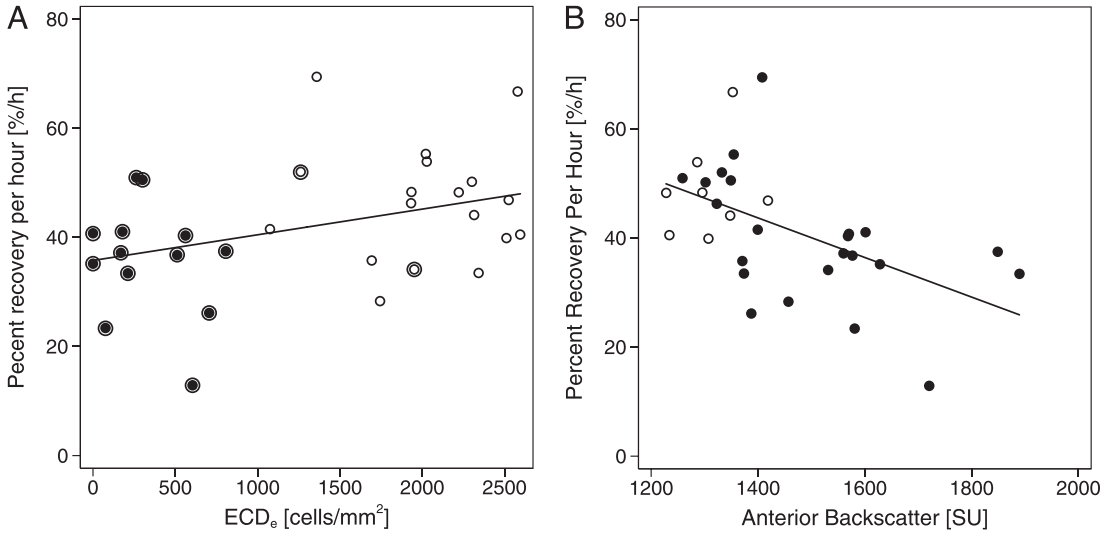

Figure 2. Association between ECD_e, anterior corneal backscatter, and corneal hydration control. Associations were determined between PRPH of central corneal thickness after induced corneal swelling and morphologic parameters at steady-state in FECD and normal corneas. (**A**) Corneas with ECD_e <1000 cells/mm^2 had a lower PRPH (36%/h; 95% CI 30–42; *closed circles*) than corneas with ECD_e >1000 cells/mm^2 (46%/h; 95% CI 41–52; $P = 0.011$; *open circles*). Corneas with clinically moderate and advanced FECD are indicated by *large overlaying circles*. (**B**) High anterior corneal backscatter was associated with worse corneal hydration control in normal (*open circles*) and FECD (*closed circles*) corneas ($r = -0.53$, $P = 0.002$). *Lines* represent the linear regression.

In our study, we defined severity of FECD according to a morphologic grading scale,[3,4] which can be easily implemented in clinical practice. Nevertheless, this grading scale is subjective, which leads to interobserver variation,[6] and does not account for the presence of subclinical corneal edema that can be present even when morphologic changes are not sufficiently advanced.[6,24] We investigated the association between corneal hydration control and various morphologic parameters, including clinical grade and its objective morphological equivalent, ECD_e,[18] corneal swelling, and corneal backscatter in an effort to provide the clinician with objective measures beyond the patient's subjective symptoms. Although all of these parameters were associated with PRPH in univariable analyses, only anterior corneal backscatter and induced swelling were associated with PRPH in a multivariable analysis. Notably, clinical grading and ECD_e, which are known to be associated,[18] and CT_{ss}, did not improve the prediction of PRPH. Because the range of normal corneal thickness is large,[25] measurements that fall within this range cannot discriminate well between normality and corneal edema, and thus it is not unexpected that corneal thickness did not improve the prediction of PRPH. Corneal thickness is still an important parameter in the evaluation of FECD, especially when measurements are thicker than the normal range, or when a change in corneal thickness can be documented.

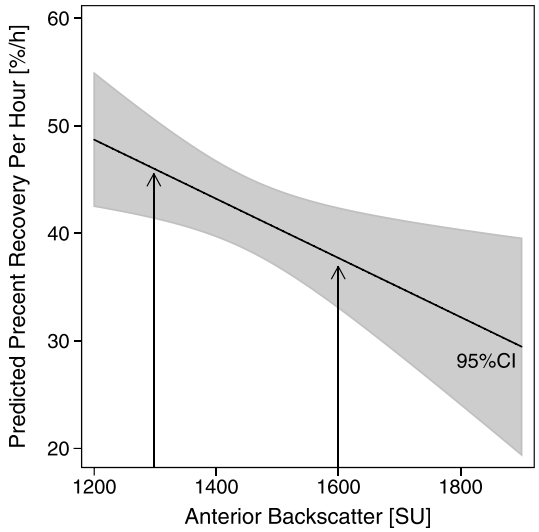

Figure 3. Predicted corneal hydration control by steady-state anterior backscatter. Predicted corneal hydration control expressed as PRPH of central thickness shown as a function of steady-state anterior backscatter assuming induced swelling of 50 μm; *gray area* represents the respective 95% CI. For example, a patient with a steady-state anterior backscatter of 1300 SU would be expected to have a PRPH of 46%/h (95% CI 42–51), whereas a patient with 1600 SU would be expected to have a PRPH of 38%/h (95% CI 33–42). Refer to the Table for typical steady-state characteristics.

Determining PRPH by the method described in this study is time-consuming and not feasible in routine clinical practice. Therefore, one of the goals of this study was to determine if any objective and easily measured variables could be used as a surrogate for corneal hydration control. Anterior corneal backscatter was the only variable that was associated with PRPH and could be measured easily and noninvasively (Fig. 3). Anterior corneal backscatter in FECD originates from edema and ultrastructural tissue changes in the basal epithelium and anterior stroma.[7,8,26] Early improvement in backscatter after restoring endothelial function has been explained by resolution of corneal edema,[27,28] suggesting that anterior backscatter is a more sensitive indicator of subtle corneal edema than is clinical examination or pachymetry. Corneal backscatter is unrelated to corneal thickness in normal (nonedematous) corneas; by combining the steady-state data in this study with previously published data from our laboratory,[7] there was no association between central corneal thickness and standardized anterior backscatter in 23 normal eyes of subjects aged 50 years or older ($r = 0.1$, $P = 0.6$). In contrast, there was a weak association between central thickness and anterior backscatter in FECD ($r = 0.3$, $P = 0.004$; $n = 88$), in which increased thickness can be attributed to corneal edema. Although there was overlap between central corneal thickness in FECD (range, 456–666 μm) and normal (range, 484–594 μm) eyes, anterior

corneal backscatter greater than 2 SDs above the normal mean was present in 8 of 29 mild, 11 of 29 moderate, and 21 of 30 advanced FECD eyes, indicating the potential discriminative value of anterior backscatter. Although the presence of corneal edema can explain the association between anterior backscatter and PRPH, the relationship was not highly predictive ($R^2 = 0.44$), possibly because a component of backscatter originates from chronic ultrastructural tissue changes and not from edema.[28] Because corneal hydration control reflects both barrier and pump function, permeability measures might improve sensitivity and prediction of true pump function.[9]

The main limitation of this study was our inability to estimate activity of the endothelial pump independent from the endothelial barrier. The PRPH provides an estimate of the net activity of both activities and pump function and can be determined only if the barrier function, based on permeability of the endothelium to a small tracer such as fluorescein, is known.[9] Unfortunately, determination of endothelial permeability to fluorescein in FECD is challenging and estimates of the barrier function have differed by a factor of 4 between studies, which led to different conclusions regarding FECD.[29,30] These variations may be from unreliable measurement of fluorescein concentration in the stroma because of increased scattered light in these corneas.[7] Also, estimates of corneal volume from central corneal thickness may be unreliable because of the abnormal thickness profile in FECD,[17] although our thickness measurements based on the entire cornea profile measured by the Scheimpflug camera were likely more representative of the cornea than thickness measured at the center by ultrasonic pachymetry. For this study, we also assumed that the difference in recovery of induced edema was solely attributed to overall endothelial function[11] and not influenced by evaporation from the anterior corneal surface. The epithelium is considerably less permeable than the endothelium, and would likely not influence this measurement significantly. Also, the epithelium of all participants remained intact during the study and the environmental conditions were controlled, minimizing potential variations in any evaporative component. The small sample size of the moderate FECD group may have limited our ability to detect a difference in PRPH from normal.

In summary, we found that corneal hydration control became impaired in advanced stages of FECD (based on morphologic grading), and that anterior corneal backscatter could provide an imperfect but notable estimate of endothelial function. Although morphologic grading is quick and simple in clinical practice, it was more helpful when penetrating keratoplasty was the procedure of choice for FECD because most surgeons waited for clinically detectable edema to be present before offering a transplant. With distinct advantages of endothelial over penetrating keratoplasty, and with knowledge that subclinical edema is present earlier in FECD, the threshold to offer a transplant has decreased. However, a simple method of estimating corneal endothelial function in these cases, in which classic biomicroscopy and pachymetric findings are not discriminatory, could help in deciding whether patients will benefit from intervention. Similarly, a simple estimate of endothelial function could be a prognostic indicator of the outcome of intraocular surgery in the setting of a compromised endothelium. Further investigation of anterior backscatter as a surrogate for endothelial function is worthwhile to better understand its role in clinical practice.

Acknowledgments

Presented in part at the annual meeting of the Association for Research in Vision and Ophthalmology, Seattle, Washington, United States, May 2016.

Supported by Research to Prevent Blindness (New York, NY, USA) (unrestricted grant to the Department of Ophthalmology and support to SVP as Olga Keith Wiess Special Scholar), Dr. Werner Jackstaedt Foundation (Wuppertal, Germany) (research fellowship to KW), Mayo Clinic Center for Translational Science Activities (Grant UL1TR000135 from the National Center for Advancing Translational Sciences, a component of the National Institutes of Health, Bethesda, MD, USA), and Mayo Foundation (Rochester, MN, USA). The funding organizations had no role in the design or conduct of this research.

Disclosure: **K. Wacker**, None; **J.W. McLaren**, None; **K.M. Kane**, None; **K.H. Baratz**, None; **S.V. Patel**, None

References

1. Wilson SE, Bourne WM. Fuchs' dystrophy. *Cornea*. 1988;7:2–18.
2. Adamis AP, Filatov V, Tripathi BJ, Tripathi RC. Fuchs' endothelial dystrophy of the cornea. *Surv Ophthalmol*. 1993;38:149–168.
3. Krachmer JH, Purcell JJ Jr, Young CW, Bucher KD. Corneal endothelial dystrophy. A study of 64 families. *Arch Ophthalmol*. 1978;96:2036–2039.
4. Louttit MD, Kopplin LJ, Igo RP Jr, et al. A multicenter study to map genes for Fuchs endothelial corneal dystrophy: baseline characteristics and heritability. *Cornea*. 2012;31:26–35.
5. Kopplin LJ, Przepyszny K, Schmotzer B, et al. Relationship of Fuchs endothelial corneal dystrophy severity to central corneal thickness. *Arch Ophthalmol*. 2012;130:433–439.
6. Repp DJ, Hodge DO, Baratz KH, McLaren JW, Patel SV. Fuchs' endothelial corneal dystrophy. Subjective grading versus objective grading based on the central-to-peripheral thickness ratio. *Ophthalmology*. 2013;120:687–694.
7. Wacker K, McLaren JW, Amin SR, Baratz KH, Patel SV. Corneal high-order aberrations and backscatter in Fuchs endothelial corneal dystrophy. *Ophthalmology*. 2015;122:1645–1652.
8. Amin SR, Baratz KH, McLaren JW, Patel SV. Corneal abnormalities early in the course of Fuchs' endothelial dystrophy. *Ophthalmology*. 2014;121:2325–2333.
9. Bourne WM, Hodge DO, McLaren JW. Estimation of corneal endothelial pump function in long term contact lens wearers. *Invest Ophthalmol Vis Sci*. 1999;40:603–611.
10. Polse KA, Brand R, Mandell R, Vastine D, Demartini D, Flom R. Age differences in corneal hydration control. *Invest Ophthalmol Vis Sci*. 1989;30:392–399.
11. Bourne WM. Clinical estimation of corneal endothelial pump function. *Trans Am Ophthalmol Soc*. 1998;96:229–242.
12. Cohen SR, Polse KA, Brand RJ, Bonanno JA. The association between pH level and corneal recovery from induced edema. *Curr Eye Res*. 1995;14:349–355.
13. Leung BK, Bonanno JA, Radke CJ. Oxygen-deficient metabolism and corneal edema. *Prog Retin Eye Res*. 2011;30:471–492.
14. Polse KA, Brand RJ, Vastine DW, Demartini DR, Sanders TL. Clinical assessment of corneal hydration control in Fuchs' dystrophy. *Optom Vis Sci*. 1991;68:831–841.
15. Mandell RB, Polse KA, Brand RJ, Vastine D, Demartini D, Flom R. Corneal hydration control in Fuchs' dystrophy. *Invest Ophthalmol Vis Sci*. 1989;30:845–852.
16. Nielsen E, Ivarsen A, Erlandsen M, Hjortdal J. Evaluation of endothelial pump function in Fuchs endothelial dystrophy before and after endothelial keratoplasty. *Cornea*. 2016;35:878–883.
17. Wacker K, McLaren JW, Patel SV. Directional posterior corneal profile changes in Fuchs' endothelial corneal dystrophy. *Invest Ophthalmol Vis Sci*. 2015;56:5904–5911.

18. McLaren JW, Bachman LA, Kane KM, Patel SV. Objective assessment of the corneal endothelium in Fuchs' endothelial dystrophy. *Invest Ophthalmol Vis Sci*. 2014;55:1184–1190.
19. McLaren JW, Bourne WM, Patel SV. Standardization of corneal haze measurement in confocal microscopy. *Invest Ophthalmol Vis Sci*. 2010;51:5610–5616.
20. McLaren JW, Wacker K, Kane KM, Patel SV. Measuring corneal haze by using Scheimpflug photography and confocal microscopy. *Invest Ophthalmol Vis Sci*. 2016;57:227–235.
21. O'Neal MR, Polse KA. In vivo assessment of mechanisms controlling corneal hydration. *Invest Ophthalmol Vis Sci*. 1985;26:849–856.
22. Maurice DM. The location of the fluid pump in the cornea. *J Physiol*. 1972;221:43–54.
23. Hodson S. Corneal stromal swelling. *Prog Retin Eye Res*. 1997; 16:99–116.
24. Kopplin LJ, Przepyszny K, Schmotzer B, et al. Relationship of Fuchs endothelial corneal dystrophy severity to central corneal thickness. *Arch Ophthalmol*. 2012;130:433–439.
25. Doughty MJ, Zaman ML. Human corneal thickness and its impact on intraocular pressure measures: a review and meta-analysis approach. *Surv Ophthalmol*. 2000;44:367–408.
26. Patel SV, Baratz KH, Hodge DO, Maguire LJ, McLaren JW. The effect of corneal light scatter on vision after Descemet stripping with endothelial keratoplasty. *Arch Ophthalmol*. 2009;127:153–160.
27. Baratz KH, McLaren JW, Maguire LJ, Patel SV. Corneal haze determined by confocal microscopy two years after Descemet stripping with endothelial keratoplasty for Fuchs corneal dystrophy. *Arch Ophthalmol*. 2012;130:868–874.
28. Patel SV, McLaren JW. In vivo confocal microscopy of Fuchs endothelial dystrophy before and after endothelial keratoplasty. *JAMA Ophthalmol*. 2013;131:611–618.
29. Burns RR, Bourne WM, Brubaker RF. Endothelial function in patients with cornea guttata. *Invest Ophthalmol Vis Sci*. 1981; 20:77–85.
30. Wilson SE, Bourne WM, O'Brien PC, Brubaker RF. Endothelial function and aqueous humor flow rate in patients with Fuchs' dystrophy. *Am J Ophthalmol*. 1988;106:270–278.

Investigative Ophthalmology & Visual Science