Predicting the Prognosis of Fuchs Endothelial Corneal Dystrophy by using Scheimpflug Tomography

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Abbreviations: FECD, Fuchs Endothelial Corneal Dystrophy; CCT, central corneal thickness; EK, endothelial keratoplasty; HR, hazard ratio.
Abstract

Purpose: To determine if Scheimpflug tomography pachymetry map and posterior elevation map patterns, central corneal thickness (CCT), and corneal backscatter can predict the prognosis of Fuchs endothelial corneal dystrophy (FECD).

Design: Cross-sectional study with follow-up of outcomes.

Participants: Ninety-six eyes (56 subjects) with a range of severity of FECD.

Methods: Corneas were graded by cornea specialists according to the area and confluence of guttae and the presence of clinically-definite edema. Masked and randomized Scheimpflug imaging pachymetry map and posterior elevation map patterns were assessed by one observer for loss of regular isopachs, displacement of the thinnest point of the cornea, and the presence of posterior surface depression. The prognosis of eyes over a 5-year (median) follow-up period was determined based on FECD progression (new onset of clinically-definite edema or ≥5% increase in CCT) or intervention by endothelial keratoplasty. Cumulative probabilities of progression/intervention were estimated from survival analyses with risk factors determined by using Cox proportional hazards models.

Main Outcome Measures: Pachymetry map and posterior elevation map patterns, corneal backscatter, and CCT (ultrasonic pachymetry).

Results: In univariable analyses, loss of regular isopachs (hazard ratio [HR], 23.07) displacement of the thinnest point (HR, 16.10), focal posterior surface depression (HR, 14.07), anterior corneal backscatter (HR, 1.22, per 1 grayscale unit-increment), and CCT (HR, 1.69, per
25 µm-increment), were risk factors for progression/intervention (p≤0.002). In multivariable analyses, loss of regular isopachs (HR 7.83, p<0.001) and displacement of the thinnest point (HR 4.86, p=0.006) were independent and clinically-important risk factors for progression/intervention. The 5-year cumulative risk of disease progression/intervention was 7%, 48%, and 89% when none, 1 or 2, and all 3 pachymetry map and posterior elevation map parameters were present, respectively (p<0.001). The 4-year cumulative risk of disease progression/intervention after uncomplicated cataract surgery was 0%, 50%, and 75% when none, 1 or 2, and all 3 pachymetry map and posterior elevation map parameters were present, respectively (p<0.001).

Conclusions: Three Scheimpflug tomography pachymetry map and posterior elevation map patterns can predict FECD prognosis independent of CCT. The risk of FECD progression/intervention, including after uncomplicated cataract surgery, increases according to the number of parameters present.
Fuchs endothelial corneal dystrophy (FECD) affects approximately 5% of the United States population and can lead to corneal edema and poor vision. Progressive corneal thickening develops gradually with a period of subclinical edema (which we define as edema that is not clinically obvious on slit lamp biomicroscopy) that can cause symptoms of glare and subjective lack of clarity in vision (i.e. subclinical edema is not necessarily asymptomatic).\textsuperscript{1-3} Although the diagnosis of FECD is easy to make clinically by detecting the presence of guttae by slit lamp examination, detecting the presence of subclinical corneal edema is more challenging. The latter is important in general ophthalmology as these patients can present with symptoms related to subclinical corneal edema, and they may need counseling regarding the risk of FECD progression, including in the setting of cataract surgery.

Currently there are no simple indicators of disease prognosis for FECD in clinical practice, and prognosis is frequently based on subjective clinical judgment. Methods have been proposed for determining whether to perform cataract surgery alone or in combination with keratoplasty in the setting of FECD, including assessing absolute central corneal thickness (CCT)\textsuperscript{4,5} and endothelial cell density,\textsuperscript{6} but these measurements are misleading for clinical decision-making.\textsuperscript{1,7} An increase in CCT over time can indicate disease progression but needs to be considered in the context of corneal thickness prior to disease onset. A cutoff of corneal backscatter measured by confocal microscopy has also been suggested to help with surgical-decision making,\textsuperscript{5} though this method is difficult to perform in clinical practice.

Recently we described a Scheimpflug imaging classification of FECD that categorizes the disease into having clinically obvious edema (edema visible by slit-lamp examination with thickening of the stroma, Descemet or deep stromal folds, stromal clouding determined by sclerotic scatter, microcystic epithelial edema or bedewing, or subepithelial bullae), subclinical corneal edema (based on the presence of specific tomographic features, see below), or no edema (absence of the specific tomographic features of edema), independent of CCT.\textsuperscript{1} We found that three tomographic pachymetry map and posterior elevation map patterns, specifically
the presence of irregular isopachs, displacement of the thinnest point of the cornea, and focal posterior surface depression, were present in FECD with subclinical corneal edema. The classification recommended that the diagnosis of FECD be made clinically with slit lamp biomicroscopy and further categorized by using Scheimpflug tomography when corneal edema was not clinically obvious. In the present study, we determined Scheimpflug tomographic pachymetry and elevation map patterns in a cohort of patients with FECD and reviewed their outcomes over a median follow-up period of five years to determine their prognosis. We included patients with a range of severity of FECD from having few scattered guttae to clinically obvious corneal edema. In addition we assessed the utility of CCT measured by ultrasound, and non-standardized corneal backscatter measurements for determining the prognosis of the disease.

Methods

Participants

Participants with a range of severity of FECD were recruited from the cornea service at Mayo Clinic (Rochester, MN, USA) between July 2012 and December 2014. The diagnosis of FECD was made by cornea specialists (SVP, KHB) based on the presence of guttae, and disease severity was graded according to the distribution of guttae and the presence of clinically-obvious edema. FECD was graded by using a modified Krachmer scale. Exclusion criteria were the presence of previous or current corneal pathology except FECD, prior corneal surgery, and prior intraocular surgery with the exception of uncomplicated phacoemulsification with endocapsular intraocular lens placement (eyes undergoing cataract surgery within 1 month of enrollment were excluded). Although we did not exclude eyes with clinically obvious corneal edema to determine if our imaging classification could predict the outcome in these eyes (i.e. positive controls), we analyzed the results with and without including this group of eyes. If eligible, both eyes of each participant were included. The study was approved by the Mayo
Clinic Institutional Review Board and adhered to the tenets of the Declaration of Helsinki; informed consent was obtained from all subjects. Some data from this cohort, related to corneal backscatter measured by using confocal microscopy, have been reported previously.9

Scheimpflug Imaging and Tomography Evaluation

All participants underwent Scheimpflug imaging (Pentacam HR; Oculus, Lynnwood, WA, USA) as previously described.10 Images were acquired at any time during routine clinic hours (7.30am to 4.30pm) with 75% of all images acquired before 1.00pm. The “4 Maps Refractive” display of enrolled eyes derived from the instrument’s software (Pentacam version 1.21r43) was exported as a high-resolution image, as described previously; only images meeting the instrument’s software quality criteria were included. De-identified images were presented in random order to one masked observer (SVP) for assessment of the pachymetry map, for loss of regular isopachs and displacement of the thinnest point of the cornea, and the posterior elevation map for posterior surface depression (the “elevation map” indicates elevation or depression, i.e. negative elevation, of the corneal surface relative to a best-fit sphere)1 (Figure 1). Loss of regular isopachs was defined as any single line of equal thickness not being almost circular/oval or parallel to adjacent isopachs within the central 4 mm of the cornea. Displacement of the thinnest point of the cornea was defined as being located outside of the inferotemporal quadrant,11 centered at the pupil center, or more than 1 mm from the pupil center in any quadrant. Focal posterior depression, i.e. protrusion of the posterior corneal surface towards the anterior chamber, was defined as any isolated area of negative elevation relative to the best fit sphere within the central 4 mm of the cornea. Each feature was determined to be either present or absent.

Non-standardized (i.e. unadjusted) corneal backscatter measurements (termed “densitometry” by the manufacturer of the instrument) from the central 2 mm-diameter area of the cornea were directly exported by using the instrument’s software. Backscatter
measurements were available for the anterior 120 µm of the cornea, mid-cornea, and posterior 60 µm of the cornea. Although we have previously advocated for standardizing corneal backscatter measurements to account for any variation in the instrument’s light source intensity or camera sensitivity between examinations, we deliberately did not adjust backscatter measurements in order to mimic a simplified assessment of backscatter (i.e. one that can be made relatively easily in clinical practice) that could be implemented if found to be of value.

Clinical Outcomes

The prognosis of enrolled eyes was determined by review of medical records from the time of Scheimpflug image acquisition to last follow-up. The time between Scheimpflug image acquisition and the onset of any of three specific outcomes was used to assess prognosis. The first outcome was a decision or recommendation to intervene with endothelial keratoplasty (EK), either because of the presence of definite corneal edema or because of vision symptoms attributed to subclinical edema. The second outcome was progression of FECD determined by the new onset of clinically-definite corneal edema. The third outcome was progression of FECD determined by an increase in CCT ≥5% (sustained over at least 2 consecutive examinations on different days or subsequently associated with clinically-definite edema) measured by using ultrasonic pachymetry (Pachette 2; DGH Technology, Exton, PA, USA) compared to the enrollment study visit.

Statistical Analysis

Demographic and enrollment data were summarized descriptively. Prognosis (progression or intervention) was estimated using the Kaplan-Meier (survival analysis) method, and prognostic risk factors for these endpoints were assessed by using univariable and multivariable Cox proportional hazards models. All estimates from the Cox models were evaluated using
sandwich estimators of the standard errors to account for including fellow eyes of the patient.

Optimal cutoff values for CCT and anterior corneal backscatter were determined statistically based on the sample. Analyses were performed for all available eyes (n=96) and also repeated for eyes without clinically-obvious corneal edema (n=81), i.e. FECD grade 6 eyes were excluded as the prognosis of these eyes might be deemed obvious from clinical examination. Analyses accounted for the timing of any cataract surgery before or after Scheimpflug imaging. A two-tailed probability of <5% was considered statistically significant.

Results

Ninety-six eyes of 56 subjects were enrolled in the study (Table 1); age at enrollment was 68 ± 15 years (mean ± standard deviation) and 37 (66%) subjects were female. Fifteen eyes had clinically obvious corneal edema present at enrollment (and were designated as grade 6). Median follow-up was 60 months (interquartile range, 45-72 months). Of the 16 fellow eyes not enrolled in this study, 9 had undergone previous EK, 4 had had cataract surgery within the previous month, and 3 were not included by patient choice (because eyes underwent more testing than just Scheimpflug imaging\(^9\)).

During the follow-up period, intervention by EK was not recommended and progression did not occur in 54 eyes. Of these 54 eyes, 12 were pseudophakic at enrollment (cataract surgery occurred at a median of 32 months prior to enrollment), 20 underwent uncomplicated cataract surgery (at a median of 13 months after enrollment), and 22 remained phakic throughout the follow-up period. For the 20 eyes that underwent cataract surgery after enrollment, the median follow-up after cataract surgery was 41 months.

Intervention by EK was recommended or progression was noted in the remaining 42 eyes; 23 eyes had existing or new-onset of clinically obvious edema, 14 eyes had a ≥5% increase in CCT, and 5 were recommended to undergo EK because of vision symptoms. The cumulative probability of disease progression or intervention at 5 years was 49% (95% CI, 36-59%) for the
group overall. Of the 42 eyes that underwent intervention or progression, 8 eyes were pseudophakic at enrollment (cataract surgery occurred at a median of 29 months prior to enrollment), 7 eyes underwent uncomplicated cataract surgery without EK (at a median of 13 months after enrollment), 23 eyes underwent combined cataract surgery with EK (at a median of 6 months after enrollment), and 4 remained phakic throughout the follow-up period. For the 7 eyes that underwent cataract surgery without EK after enrollment, all subsequently underwent EK or progression with a median interval of 18 months after cataract surgery.

Pachymetry Map and Elevation Map Patterns

In univariable analyses, all three tomographic pachymetry map and posterior elevation map patterns at enrollment were significantly associated with disease progression or intervention, regardless of whether grade 6 eyes were included or not (Table 2, Figure 2). Of the 15 eyes with grade 6 FECD at baseline, all had loss of regular isopachs, displacement of the thinnest point of the cornea, and focal posterior depression present (Table 1) at enrollment. When excluding grade 6 eyes, the cumulative risk of disease progression or intervention over 5 years was 82% (95% CI, 50-93%) for loss of regular isopachs, 78% (95% CI, 55-89%) for displacement of the thinnest point, and 77% (95% CI, 51-89%) for focal posterior depression. The cumulative risk of disease progression or intervention over 5 years increased according to the number of parameters present, from 7% (95% CI, 0-16%), when none of the pachymetry map and posterior elevation map features were present, to 48% (95% CI, 9-70) when any 1 or 2 of the features were present, to 89% (95% CI, 60-97%) when all three features were present (p<0.001, grade 6 eyes excluded, Figure 3).

In a multivariable analysis with grade 6 eyes excluded, irregular isopachs (HR 8.66; 95%CI, 2.65-28.32, p<0.001) and displacement of the thinnest point (HR 4.19; 95%CI, 1.13-15.48, p=0.03) were independent risk factors for progression/intervention, whereas focal posterior
depression was not (HR 0.95; 95%CI, 0.37-2.45, p=0.92). However, when excluding irregular isopachs from the multivariable model, focal posterior depression was an independent risk factor for progression/intervention (HR 3.93; 95%CI, 1.20-12.85, p=0.02).

**Corneal Thickness and Backscatter**

In univariable analyses, anterior, mid, and posterior backscatter were all associated with disease progression or intervention (Table 2); CCT was associated with disease progression or intervention when grade 6 eyes were included but not when they were excluded (Table 2). In a multivariable analysis of all eyes that included CCT and all backscatter parameters, only anterior corneal backscatter was an independent risk factor for disease progression or intervention when grade 6 eyes were included (HR 1.18; 95%CI, 1.07-1.29, p<0.001) or excluded (HR 1.30; 95%CI, 1.09-1.54, p=0.003).

FECD progression or intervention was estimated according to sample-specific optimal cutoff values for CCT and anterior corneal backscatter (see supplemental figure available at http://www.aaojournal.org). After excluding grade 6 eyes, the cumulative risk of disease progression or intervention at 5 years was 54% (95% CI, 32-69%) for eyes with CCT greater than or equal to the sample-specific optimal cutoff and 25% (95% CI, 9-38%) for CCT less than the sample-specific optimal cutoff (HR, 2.36, [95% CI, 1.06-5.25], p=0.036). After excluding grade 6 eyes, the cumulative risk of disease progression or intervention at 5 years was 85% (95% CI, 56-95%) when anterior corneal backscatter was greater than or equal to the sample-specific optimal cutoff and 20% (95% CI, 8-31%) when less than the sample-specific optimal cutoff (HR, 7.33, [95% CI, 3.34, 16.07], p<0.001).

**Combined Analyses**

In multivariable analyses that combined pachymetry map and posterior elevation map patterns with backscatter or CCT, anterior corneal backscatter and CCT were independent but
weak risk factors for disease progression or intervention compared to loss of regular isopachs and displacement of the thinnest point (Table 3). Similar results were found whether grade 6 eyes were included or not (Table 3).

Prognosis after cataract surgery

Twenty-seven eyes underwent uncomplicated cataract surgery after enrollment in the study. The 4-year cumulative risk of disease progression/intervention after uncomplicated cataract surgery was 0%, 50% (95% CI, 0-78%), and 75% (95% CI, 17-93%), when none, 1 or 2, and all 3 pachymetry map and posterior elevation map parameters were present, respectively (p<0.001, Figure 4).

Discussion

Assessment of three pachymetry map and posterior elevation map patterns derived from Scheimpflug tomography of corneas with FECD predicted disease prognosis independent of CCT. The cumulative probability of disease progression or intervention over 5 years increased from 7% when none of the patterns were present to 89% when all were present. The number of parameters present also predicted FECD prognosis after uncomplicated cataract surgery. The findings are important for counseling patients about their prognosis, and can also help identify patients at risk of progression for enrollment in clinical trials.

We recently described a revised classification of FECD that combined clinical examination and Scheimpflug imaging.¹ FECD can be classified as having clinically-definite corneal edema, subclinical edema, or no edema, based on the presence of three pachymetry map and posterior elevation map patterns. In this study, we determined the presence of these specific patterns that signify clinical or subclinical corneal edema in a cohort of eyes with a range of severity of FECD and determined their outcomes over a median follow-up period of 5 years. In univariable analyses, loss of regular isopachs, displacement of the thinnest point of the cornea, and focal
posterior depression were all associated with a higher risk of disease progression or intervention whether eyes with clinically-definite corneal edema were included or not. A multivariable analysis of all three parameters and cataract surgery (if performed) found that only loss of regular isopachs and displacement of the thinnest point were independent risk factors for progression, conferring an 8- and 4-fold increased risk of progression, respectively. Because the pachymetry map is derived from anterior and posterior elevation data, it is not surprising that focal posterior depression was not an independent risk factor; after excluding irregular isopachs from the multivariable model, focal posterior depression was in fact a significant risk factor, indicating the correlation between the two risk factors. Therefore, we still recommend interpreting pachymetry and posterior elevation map maps together as the patterns in each map should complement each other, i.e. the region of posterior depression should correspond to the region of thickening of the cornea with irregular isopachs (Figure 1), and because the cumulative probability of disease progression or intervention over 5 years increased according to the number of these parameters that were present (7% when none were present, 48% when any one or two of the patterns were present, and 89% when all three were present).

Different cutoff values for CCT have been previously proposed for when to consider cataract surgery combined with keratoplasty. We have recommended not basing such treatment decisions on CCT and to assess pachymetry map and posterior elevation map patterns instead. In this study, we found that the risk of disease progression/intervention over 4 years after uncomplicated cataract surgery increased according to the number of pachymetry map and posterior elevation map patterns present (0% when none were present, 50% when any one or two of the patterns were present, and 75% when all were present), similar to the group overall and supporting our previous recommendation. In terms of prognosis for the overall group, CCT was a weak predictor of prognosis relative to the pachymetry map and posterior elevation map parameters (Table 3), especially when clinically-definite edema was not visible (1 in 4 eyes with CCT less than the sample-specific optimal cutoff progressed or needed
The present study further supports that an isolated measurement of CCT is not a helpful parameter for assessing FECD.

Corneal backscatter increases in FECD because of the presence of corneal edema and also because of structural changes in response to chronic edema; it also correlates with, but is poorly predictive of, corneal endothelial function. In these previous studies, we standardized corneal backscatter measurements to eliminate any confounding effect introduced by variations in the light source and camera of the instrument. Standardizing backscatter measurements requires imaging a fixed scatter source ("standard") prior to every examination followed by adjustment of corneal measurements relative to the image intensity of the standard (which should remain the same over time). Unfortunately, this standardization step is not built into the instrument and therefore requires additional effort and external manipulation of the data, which is neither quick nor simple for routine clinical practice. In this study, we deliberately did not use standardized backscatter measurements to determine whether raw backscatter data from the instrument, which is easily available for clinical practice (and frequently but incorrectly used in investigational studies), might assist in predicting disease progression. We found that non-standardized anterior corneal backscatter was an independent but weak predictor of FECD progression/intervention in multivariable analyses. However, with the hazard ratio being small (and very close to 1) relative to those for loss of regular isopachs and displacement of the thinnest point, and the difficulty in standardizing measurements, anterior corneal backscatter adds very little additional clinical value for predicting FECD prognosis.

The strengths of this study include the standardized manner in which these eyes were evaluated by two cornea surgeons (SVP, KHB) involved in programmatic research of FECD. In addition, median follow-up for all eyes was 5 years and three-quarters of all eyes had ≥ 45 month of follow-up, which helped provide meaningful prognostic information. Limitations of this study include the relatively small sample size; although this resulted in relatively wide
confidence intervals for some analyses, the lower limit of the confidence intervals for loss of
regular isopachs and displacement of the thinnest point of the cornea were still of high clinical
importance. Only 27 eyes underwent cataract surgery (without concurrent EK) after enrollment,
and while the presence of abnormal pachymetry map and posterior elevation map patterns
significantly predicted disease progression or intervention over 4 years, a larger series is
needed to quantify this risk after cataract surgery more precisely. In addition, Scheimpflug
images and ultrasonic pachymetry were not acquired at a standardized time of day given that
corneal edema is usually worse in the morning; nevertheless, our data were representative of
typical clinical practice when patients with FECD might be seen at any time of day. Finally, it is
unknown whether the mildest cases of subclinical edema can be detected by tomography or if
tomography is helpful for clinical decision-making if vision is affected by guttae in the absence of
edema. However, we are unaware of carefully designed studies that show a benefit of EK when
vision is assumed to be affected by guttae in the absence of edema; this deserves further
investigation and could require revision of our FECD classification.

The findings of this study support using the revised classification of FECD, which is a more
functional classification compared to morphologic grading of guttae distribution. This
classification is simple to use in clinical practice, requiring slit-lamp confirmation of FECD and
exclusion of other corneal pathologies followed by Scheimpflug imaging to assess for subclinical
edema.¹ Pachymetry map and posterior elevation map interpretation is familiar to many
ophthalmologists when assessing for corneal ectasia, and thus the method can be easily
implemented in many practices (Figure 1) and does not require external data manipulation
(like assessing corneal backscatter). The presence of even 1 or 2 of the pachymetry map and
posterior elevation map features increases the probability of FECD progression or intervention,
and suggests that subclinical edema is already present. We strongly recommend assessing for
these pachymetry map and posterior elevation map patterns in FECD when patients complain of
visual symptoms that might be attributable to the disease, or when patients might require
cataract surgery. This method is of higher clinical relevance than simply measuring CCT, especially when a patient has not been previously evaluated for FECD and when corneal edema is not clinically obvious. In addition, as novel treatments for FECD are being investigated,\textsuperscript{22,23} evaluating pachymetry map and posterior elevation map patterns should be considered for future interventional clinical trials as this method can help define the disease state and identify eyes at risk of progression.\textsuperscript{7}
References


Figure Legends

Figure 1: Scheimpflug tomography pachymetry (left) and posterior elevation (right) maps of the same eye with Fuchs endothelial corneal dystrophy in 2012 (upper) and 2019 (lower). Pachymetry maps were evaluated for loss of parallel/almost circular isopachs and for displacement of the thinnest point (circle) from the inferotemporal quadrant relative to the pupil center (+). Posterior elevation maps were evaluated for negative elevation, i.e. depression, relative to the best-fit sphere. In 2012, tomography showed subtle evidence of subclinical edema with gradual progression of tomographic findings through 2019; note the same location of irregular isopachs and posterior depression at both examinations. Clinically-obvious corneal edema was not present by slit-lamp examination at any stage, and central corneal thickness (CCT) only increased slightly between examinations (545 µm to 560 µm). After DMEK (not shown), CCT decreased to 476 µm and visual acuity improved to 20/20.

Figure 2: Cumulative probability of progression/intervention for Fuchs endothelial corneal dystrophy (FECD) based on loss of regular isopachs, displacement of the thinnest point of the cornea, and presence of focal posterior depression; eyes with visible corneal edema (grade 6) were excluded (n=81). Univariable hazard ratios (HR) are shown and were determined from Cox models.

Figure 3: Cumulative probability of progression/intervention for Fuchs endothelial corneal dystrophy (FECD) based on the number of pachymetry map and posterior elevation map patterns present for all eyes (left, n=96) and after excluding (grade 6) eyes with visible corneal edema (right, n=81). The cumulative risk of disease progression/intervention over 5 years was 7%, 48%, and 94% (latter 89% if grade 6 excluded) when none, 1 or 2, and all 3 pachymetry map and posterior elevation map parameters were present, respectively (p<0.001).
Figure 4: Cumulative probability of progression/intervention for Fuchs endothelial corneal dystrophy after uncomplicated cataract surgery (n=27). The cumulative risk of disease progression/intervention over 4 years was 0%, 50%, and 75% when none, 1 or 2, and all 3 pachymetry map and posterior elevation map parameters were present, respectively (p<0.001).
## Table 1: Characteristics of eyes at enrollment

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<tr>
<th>Fuchs Endothelial Corneal Dystrophy Grade</th>
<th>1-2</th>
<th>3-4</th>
<th>5</th>
<th>6</th>
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<tbody>
<tr>
<td>Eyes (n)</td>
<td>30</td>
<td>34</td>
<td>17</td>
<td>15</td>
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<tr>
<td>Median Age, yrs (range)</td>
<td>73 (53-87)</td>
<td>63 (42-89)</td>
<td>63 (42-81)</td>
<td>69 (45-89)</td>
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<td>Phakic, n (%)</td>
<td>22 (73)</td>
<td>27 (79)</td>
<td>13 (76)</td>
<td>14 (93)</td>
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<tr>
<td>Loss of parallel isopachs, n (%)</td>
<td>9 (30)</td>
<td>12 (35)</td>
<td>12 (71)</td>
<td>15 (100)</td>
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<tr>
<td>Displacement of the thinnest point, n (%)</td>
<td>6 (20)</td>
<td>9 (26)</td>
<td>14 (82)</td>
<td>15 (100)</td>
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<td>Focal posterior depression, n (%)</td>
<td>10 (33)</td>
<td>11 (32)</td>
<td>13 (76)</td>
<td>15 (100)</td>
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<td>Number of tomographic features</td>
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<td>0</td>
<td>19 (63)</td>
<td>21 (62)</td>
<td>2 (12)</td>
<td>0 (0)</td>
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<td>1 or 2</td>
<td>7 (23)</td>
<td>6 (18)</td>
<td>5 (29)</td>
<td>0 (0)</td>
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<tr>
<td>3</td>
<td>4 (13)</td>
<td>7 (21)</td>
<td>10 (59)</td>
<td>15 (100)</td>
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<tr>
<td>Central Corneal Thickness [µm], mean ± SD (range)</td>
<td>560 ± 27</td>
<td>573 ± 35</td>
<td>571 ± 43</td>
<td>618 ± 33</td>
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<td>Corneal Backscatter [grayscale], mean ± SD (range)</td>
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<td>Anterior 120 µm</td>
<td>27.9 ± 2.7</td>
<td>28.2 ± 2.6</td>
<td>32.2 ± 5.3</td>
<td>35.6 ± 5.7</td>
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<td></td>
<td>(23.2-34.2)</td>
<td>(23.6-34.9)</td>
<td>(23.7-42.5)</td>
<td>(27.6-46.7)</td>
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<td>Mid cornea</td>
<td>17.3 ± 1.7</td>
<td>16.9 ± 1.5</td>
<td>19.6 ± 3.2</td>
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<td></td>
<td>(14.4-21.1)</td>
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<td>Posterior 60 µm</td>
<td>12.0 ± 2.3</td>
<td>12.5 ± 2.2</td>
<td>16.2 ± 4.1</td>
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<td>(8.6-18.7)</td>
<td>(9.1-17.8)</td>
<td>(11.2-27.6)</td>
<td>(11.9-25.6)</td>
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FECD grades: ≤12 scattered guttae (grade 1); >12 scattered guttae (grade 2); confluent guttae with widest diameter ≤2 mm (grade 3), 2-5 mm (grade 4), >5 mm (grade 5); presence of clinically definite corneal edema (grade 6).
Table 2: Univariable Cox proportional hazard ratios for risk factors for Fuchs endothelial corneal dystrophy (FECD) progression or intervention.

<table>
<thead>
<tr>
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<th>All eyes (n=96)</th>
<th>Grade 6 eyes excluded (n=81)</th>
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<tr>
<td></td>
<td>Hazard Ratio</td>
<td>P</td>
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<td></td>
<td>(95% CI)</td>
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<td>Pachymetry Map and Posterior Elevation Map Patterns</td>
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<td>Loss of Regular Isopachs</td>
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<tr>
<td></td>
<td>(8.39-63.40)</td>
<td></td>
</tr>
<tr>
<td>Displacement of the Thinnest Point of the Cornea</td>
<td>16.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>(6.33-40.90)</td>
<td></td>
</tr>
<tr>
<td>Focal Posterior Depression</td>
<td>14.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>(5.61-35.24)</td>
<td></td>
</tr>
<tr>
<td>Corneal Backscatter (per 1 grayscale unit-increment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior 120 µm of cornea</td>
<td>1.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>(1.16-1.28)</td>
<td></td>
</tr>
<tr>
<td>Mid cornea</td>
<td>1.30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>(1.16-1.47)</td>
<td></td>
</tr>
<tr>
<td>Posterior 60 µm of cornea</td>
<td>1.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>(1.09-1.33)</td>
<td></td>
</tr>
<tr>
<td>Central Corneal Thickness (per 25 µm-increment)</td>
<td>1.69</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>(1.22-2.36)</td>
<td></td>
</tr>
</tbody>
</table>

By excluding grade 6 eyes with clinically-definite corneal edema by slit-lamp examination, analysis was confined to FECD eyes with subclinical or no edema.
Table 3: Multivariable analyses combining pachymetry map and posterior elevation map patterns with central corneal thickness (CCT) or corneal backscatter.

<table>
<thead>
<tr>
<th></th>
<th>All eyes (n=96)</th>
<th>Grade 6 eyes excluded (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>Multivariable model with CCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of Regular Isopachs</td>
<td>12.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>(4.07-38.33)</td>
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<tr>
<td>Displacement of the Thinnest Point of the Cornea</td>
<td>6.60</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>(1.88-23.13)</td>
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<tr>
<td>Focal Posterior Depression*</td>
<td>0.56</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>(0.20-1.60)</td>
<td></td>
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<tr>
<td>CCT (per 25 µm-increment)</td>
<td>1.62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>(1.30-2.01)</td>
<td></td>
</tr>
<tr>
<td>Multivariable model with Corneal Backscatter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of Regular Isopachs</td>
<td>10.25</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>(3.98-26.40)</td>
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<tr>
<td>Displacement of the Thinnest Point of the Cornea</td>
<td>3.95</td>
<td>0.02</td>
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<td>(1.24-12.58)</td>
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<tr>
<td>Focal Posterior Depression*</td>
<td>0.71</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>(0.32-1.55)</td>
<td></td>
</tr>
<tr>
<td>Anterior Corneal Backscatter (per 1 grayscale unit-increment)</td>
<td>1.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>(1.07-1.21)</td>
<td></td>
</tr>
</tbody>
</table>

*Focal posterior depression was not an independent risk factor in these multivariable models because it was highly correlated with loss of regular isopachs; when considered in a model without loss of regular isopachs, focal posterior depression was a significant risk factor and therefore should not be discounted.
2012:
- Subtle loss of regular isopachs
- Nasal displacement of thinnest point
- Early focal posterior surface depression

2019:
- Irregular isopachs
- Nasal displacement of thinnest point
- Obvious focal posterior surface depression
Loss of Parallel Isopachs
(HR=18.00, p<0.001)

Displacement of Thinnest Point
(HR=11.53, p<0.001)

Focal Posterior Depression
(HR=10.21, p<0.001)
Précis

Three pachymetry and posterior surface map patterns, easily obtained from Scheimpflug tomography in clinical practice, predict the 5-year prognosis of Fuchs endothelial corneal dystrophy, and should be incorporated into clinical evaluation of the disease.