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Corneal High-Order Aberrations and Backscatter in Fuchs' Endothelial Corneal Dystrophy

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Purpose: Suboptimal visual acuity after endothelial keratoplasty has been attributed to increased anterior corneal high-order aberrations (HOAs). In this study, we determined anterior and posterior corneal HOAs over a range of severity of Fuchs' endothelial corneal dystrophy (FECD).

Design: Cross-sectional study.

Participants: A total of 108 eyes (62 subjects) with a range of severity of FECD and 71 normal eyes (38 subjects).

Methods: All corneas were examined by using slit-lamp biomicroscopy to determine the severity of FECD versus normality. Fuchs' endothelial corneal dystrophy corneas were categorized as mild, moderate, or advanced according to the area and confluence of guttae and the presence of clinically visible edema. Normal corneas were devoid of any guttae. Wavefront errors from the anterior and posterior corneal surfaces were derived from Scheimpflug images and expressed as Zernike polynomials through the sixth order over a 6-mm diameter optical zone. Backscatter from the anterior 120 μm and posterior 60 μm of the cornea also was measured from Scheimpflug images and was standardized to a fixed scatter source. Variables were compared between FECD and control eyes by using generalized estimating equation models to adjust for age and correlation between fellow eyes.

Main Outcome Measures: High-order aberrations, expressed as root mean square of wavefront errors, and backscatter of the anterior and posterior cornea.

Results: Total anterior corneal HOAs were increased in moderate (0.61±0.27 μm, mean ± standard deviation; $P = 0.01$) and advanced (0.66±0.28 μm; $P = 0.01$) FECD compared with controls (0.47±0.16 μm). Total posterior corneal HOAs were increased in mild (0.22±0.09 μm; $P = 0.017$), moderate (0.22±0.08 μm; $P < 0.001$), and advanced (0.23±0.09 μm; $P < 0.001$) FECD compared with controls (0.16±0.03 μm). Anterior and posterior corneal backscatter were higher for all severities of FECD compared with controls ($P \leq 0.02$, anterior; $P \leq 0.001$, posterior).

Conclusions: Anterior and posterior corneal HOAs and backscatter are higher than normal even in early stages of FECD. The early onset of HOAs in FECD might contribute to the persistence of HOAs and incomplete visual rehabilitation after endothelial keratoplasty. *Ophthalmology 2015;■:1–8 © 2015 by the American Academy of Ophthalmology.*

Fuchs' endothelial corneal dystrophy (FECD) is a bilateral corneal disease characterized by focal posterior collagenous excrescences (guttae) and progressive corneal edema, resulting in reduced corneal transparency and impaired vision.[1] Corneal transplantation is the only available treatment to restore corneal transparency in advanced stages of FECD. Over the last decade, endothelial keratoplasty has become the standard method of transplantation[2] with good visual outcomes,[3,4] but visual rehabilitation seems to be limited by persistent changes in the anterior cornea[5–7] that degrade the regularity of the anterior corneal surface and increase high-order aberrations (HOAs).[5,8–10] Increased HOAs are associated with worse visual acuity, irrespective of the endothelial keratoplasty technique.[5,7–10] However, it is unknown when in the course of FECD HOAs become abnormal. Other anterior corneal abnormalities appear early in the course of the disease, including subepithelial fibroblasts,[11] keratocyte loss, and increased anterior corneal haze (or backscatter).[12] These abnormalities persist through at least 3 years after endothelial keratoplasty.[11–13] As our ability to assess and treat FECD improves with new technologies and techniques, understanding when in the course of the disease these tissues change might improve our understanding of visual limitation after endothelial keratoplasty.

In this study, we assessed changes in anterior and posterior corneal HOAs and backscatter over a range of severity of FECD and normal corneas by using Scheimpflug imaging. Noncontact Scheimpflug imaging is widely available and simple to use, and provides information about aberrations, corneal haze, and corneal thickness. We examined the relationships among HOAs, backscatter, and corneal

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morphologic characteristics that are typically altered in FECD, such as corneal thickness and effective endothelial cell density (ECD_e).[14] We hypothesized that HOAs and backscatter are increased in the anterior and posterior cornea early in FECD, and are associated with ECD_e and corneal thickness.

Methods

Subjects and Clinical Grading

All subjects were examined by cornea specialists using slit-lamp biomicroscopy. Severity of FECD was graded clinically on the basis of the area and confluence of guttae, and the presence of edema, as described previously.[15,16] Corneas with 1 to 12 or ≥12 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 >5-mm diameter of confluent guttae or any visible stromal or epithelial edema (grades 5 and 6) were considered to have advanced FECD. Corneas without guttae were considered normal (grade 0); control subjects were only enrolled if aged >40 years to match the age distribution of the disease group.[17] Exclusion criteria for all subjects were corneal pathology (other than FECD in the FECD groups), previous ocular surgery except uncomplicated phacoemulsification with posterior chamber intraocular lens implantation, or systemic or topical medication use known to affect the cornea. The Mayo Clinic Institutional Review Board prospectively approved this study; the research followed the tenets of the Declaration of Helsinki and complied with the Health Insurance Portability and Accountability Act. Informed consent was obtained from all subjects.

Corneal Aberrations

Wavefront errors over a 6-mm diameter optical zone centered at the corneal apex were determined by using a rotating Scheimpflug camera (Pentacam HR; Oculus, Lynnwood, WA). All Scheimpflug images were checked for data acquisition errors. Wavefront errors from the anterior and posterior corneal surfaces were calculated by ray-tracing (Pentacam software version 1.20r29) and expressed as Zernike polynomials through the sixth order. The root-mean-square wavefront error (μm) for coma $\sqrt{(Z_3^{-1})^2+(Z_3^1)^2}$, coma-like $\sqrt{(Z_3^{-1})^2+(Z_3^1)^2+(Z_5^{-1})^2+(Z_5^1)^2}$, trefoil $\sqrt{(Z_3^{-3})^2+(Z_3^3)^2}$, and trefoil-like $\sqrt{(Z_3^{-3})^2+(Z_3^3)^2+(Z_4^{-4})^2+(Z_4^4)^2+(Z_5^{-5})^2+(Z_5^5)^2+(Z_6^{-6})^2+(Z_6^6)^2}$ aberrations were calculated from Zernike coefficients determined by the imaging software.[18] Spherical aberration was expressed as $|Z_4^0|$. Total HOAs from the third to sixth order were summarized from the Zernike polynomials as $\sqrt{\sum_{n=3}^{6}\sum_{-m}^{m}(Z_n^m)^2}$. The software assumed the refractive index of the cornea was 1.3375.

Corneal Backscatter

Corneal haze (backscatter) was determined from Scheimpflug image brightness. Mean backscatter of a 2-mm diameter circle centered on the apex was measured for the anterior 120 μm and posterior 60 μm of the cornea. Before each examination, the image brightness of a standardized scatter source (a custom-made titanium-embedded rigid contact lens)[19] was measured to account for fluctuations in the brightness of the light source and sensitivity of the detection system over time.[20] Raw corneal image brightness was adjusted according to the brightness of the reference standard. Backscatter was expressed in scatter units (SU), the concentration of a turbidity standard, AMCO Clear (AMCO Clear; GFS Chemicals, Columbus, OH), that gave the same image brightness as the corneal image.[20,21]

Effective Endothelial Cell Density and Corneal Thickness

To account for progressive reduction of local endothelial cell density and increased area of guttae, 1 investigator (K.W.) manually determined the ECD_e.[14] Central corneal endothelial images were recorded by using confocal microscopy (ConfoScan 4; Nidek Technologies, Freemont, CA) with a 20× noncontact objective, as described previously.[14] Briefly, after several confocal scans through the endothelium, the best-quality image was chosen for analysis. Local endothelial cell density was the number of contiguous cells divided by their total area and was estimated by marking 100 adjacent cells in a circumscribed area devoid of guttae (variable frame method). The fraction of the image covered by guttae (R) in FECD subjects was estimated by using a custom image-processing program (Analyze AVW; Mayo Medical Solutions, Rochester, MN). The ECD_e was the product of local cell density and the fraction of image area that was devoid of guttae (1 − R). Central corneal thickness (CCT) was measured from the Scheimpflug images.

Statistical Analysis

Unadjusted results were summarized as mean ± standard deviation by severity of FECD. For analytic purposes, variables were compared by using generalized estimating equation (GEE) models to account for possible correlation between fellow eyes of the same subject.[22] The GEE models were used to calculate population-averaged mean differences between FECD groups with respective 95% confidence intervals (CIs). Because corneal HOAs are known to change with age,[23] we adjusted estimates for age as a continuous variable. We did not find that age affected central corneal backscatter, similar to a previous study,[24] and thus the backscatter analysis was not adjusted for age. Relationships between variables were assessed by age-adjusted Pearson correlations with significances of correlations determined by GEE models. Contingency tables were analyzed with the Fisher exact test. Analyses were considered statistically significant if $P < 0.05$. The minimum difference that could be detected, if indeed a difference existed, was calculated for nonsignificant comparisons ($\alpha = 0.05$, $\beta = 0.20$). All analyses were performed by using Stata version 13.1 (StataCorp LP, College Station, TX).

Results

Subjects

A total of 108 corneas from 62 subjects with FECD and 71 normal corneas from 38 subjects were examined; the median age was 66 years (range, 40−89 years) (Table 1). Subjects with FECD were older than controls (mean difference, 7.9 years; $P = 0.002$). Subjects with mild ($P = 0.01$) and moderate ($P = 0.03$) FECD were more often pseudophakic than controls.