Published in final edited form as:

Cornea. 2017 October ; 36(10): 1166–1171. doi:10.1097/ICO.0000000000001292.

Peripheral Endothelial Cell Count is a Predictor of Disease Severity in Advanced Fuchs' Endothelial Corneal Dystrophy

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Abstract

Purpose—In advanced Fuchs' endothelial corneal dystrophy (FECD), central endothelial changes do not correlate with disease severity. Peripheral endothelial cell count (ECC) has not been studied as a marker for FECD severity. The goal of this study is to determine the relationship between peripheral ECC and known clinical markers of FECD in advanced cases.

Methods—Patients with FECD examined between January 1, 2013 and September 1, 2016 by one cornea specialist were identified. Electronic medical records from all prior visits were reviewed to include eyes with high-quality central and peripheral *in vivo* confocal microscopy (IVCM) images performed on the same day as a clinical evaluation. Endothelial photographs were used to perform manual cell counts centrally and peripherally. Clinical grading of FECD from 1 to 4 was performed at the slit lamp.

Results—We identified 154 eyes of 126 patients that met criteria for inclusion in this study. With higher disease grades, central ECC and peripheral ECC decreased, visual acuity worsened, and central corneal thickness (CCT) increased (all $p < 0.05$). In patients with advanced disease (defined as either grade of 3 or 4, CCT > 700 , or central ECC < 350), peripheral ECC was the best predictor of disease severity and had the highest number of statistically significant correlations with other clinical markers of disease as compared to competing variables.

Conclusion—In advanced FECD, severity is best determined by peripheral ECC as compared to central ECC, visual acuity, clinical disease grade, and CCT.

Keywords

Fuchs' endothelial corneal dystrophy; confocal microscopy; peripheral endothelial cell count

Introduction

Fuchs' endothelial corneal dystrophy (FECD) is a genetically complex, age-related disorder that affects 4.5% of individuals over 50 years of age and 10.5% of patients over 60 years of

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Authors do not have any financial or proprietary interest in products, methods, or material mentioned in this article.

This work has not been previously published or presented at a meeting.

age.¹ It leads to progressive loss of corneal endothelial cells and extracellular deposits, termed guttae. These developments compromise corneal deturgescence, resulting in swelling and a loss of vision.^{2–4} Stromal edema may also correlate with keratocyte depletion of the anterior cornea.⁵

The clinical course of FECD usually spans 10–20 years.⁶ During this time, guttae formation and endothelial changes start in the central cornea and spread toward the periphery.⁷ In early stages, FECD is characterized by central guttae accompanied by a decline in central endothelial cell count (ECC) and morphological changes to the endothelial monolayer.⁷ In later stages, coalescence of guttae is accompanied by a low central endothelial cell density and compromise in endothelial barrier function, causing corneal edema. Correspondingly, the area of guttae is significantly larger in the central cornea compared with paracentral and peripheral regions.⁸

Clinical grading of FECD severity is often determined by slit lamp microscopy, central corneal thickness (CCT), and central ECC. Slit lamp grading evaluates the area of guttae coalescence and presence of edema.⁶ An additional method used to determine severity is retroillumination photography,^{9,10} which has been employed to detect formation of new guttae over time.¹¹ However, manual counting can be time-consuming. Moreover, the main limitation of central ECC is that in moderate to severe FECD, guttae replace the central endothelial monolayer and render the central ECC undetectable by most imaging modalities.¹² As such, central endothelial changes do not significantly correlate with disease grade in patients with grade 3 or higher (using a modified Krachmer grading scale).¹² To the best of our knowledge, peripheral ECC has not been studied as a marker for FECD severity in advanced cases.

In vivo confocal microscopy (IVCM) allows for a magnified view of all layers of the cornea, including the endothelium.^{13,14} IVCM can be useful in the evaluation of advanced FECD before grafting as it is able to focus on the posterior cornea despite opacification and edema.¹⁴ Furthermore, confocal microscopy is able to image the peripheral corneal endothelium circumferentially.¹⁵ In this study, we utilized Heidelberg Retina Tomograph (HRT) IVCM to detect the relationship between peripheral ECC and known clinical parameters that are currently used to denote FECD severity. We determined that peripheral ECC highly correlates with disease severity in advanced FECD, thus introducing a new imaging-based method to assess the clinical progression of FECD.

Materials and Methods

Study Population and Data Collection

Approval for this retrospective chart review was obtained from the Institutional Review Board at Massachusetts Eye and Ear Infirmary (Boston, MA, USA). The investigators recorded data in such a manner that subjects could not be identified, either directly or through linked identifiers.

We identified all patients with FECD examined at any point between January 1, 2013 and September 1, 2016 by one cornea specialist (UVJ). The electronic medical records and

IVCM imaging results (including dates prior to January 1, 2013) of the patients were reviewed to include only those patients with IVCM performed on the same day as a clinic visit and with IVCM studies including high quality central and peripheral endothelial imaging. Patients were excluded from this study if IVCM image quality was poor in central or peripheral endothelial photographs, or if the patient did not have a complete clinical examination on the same day as IVCM imaging that included refraction, slit lamp examination, and pachymetry. In cases where both eyes of a patient qualified for inclusion, the two were included for separate analyses. In situations where a patient had multiple clinic visits in which the required data was available, the most recent date was selected for inclusion in this study.

The laser scanning confocal microscope (HRT3 with Rostock Corneal Module [RCM], Heidelberg Engineering, Heidelberg, Germany) was used to obtain endothelial images and to perform manual cell counts centrally and peripherally. HRT3 images that were chosen to determine ECC for each eye had to be high resolution and have a countable mosaic of endothelial cells homogeneously distributed throughout a scanned area of $400 \times 400 \mu\text{m}$ per image. A region of interest (ROI) with a minimum area of 0.03 mm^2 was defined on the original image and the number of cells within that outline was manually counted. A sample endothelial image from a healthy eye with an ROI outlined with manual count is presented in Figure 1. In cases of advanced FECD with very few remaining endothelial cells, a representative ROI was selected to allow for at least a single countable cell, therefore allowing us to quantify a value for ECC. Subjects were instructed by the imaging technician to look in a direction off-center to obtain a peripheral endothelial photograph, which was captured 2 to 3 mm inside the limbus.

Data collected on each patient included date of birth, date of visit, age at date of visit, months of follow up, gender, eye, central ECC, peripheral ECC, directional location of peripheral ECC, logarithm of the minimum angle of resolution (LogMAR) best corrected visual acuity (BCVA), clinical grade, CCT, future need for surgery, and type of surgery performed. Clinical grading of FECD was performed at the slit lamp according to the following guidelines: grade 1 – nonconfluent guttae; grade 2 – presence of any area of confluent guttae, but without edema or clinical thickening; grade 3 – confluent guttae with edema or clinical thickening; grade 4 – edema associated with whitening or haze. For eyes with visual acuity in the counting fingers range, acuity was documented as 20/400 for LogMAR conversions. To limit observer bias, the investigator who reviewed electronic medical records (JAT) was different than the researcher who performed manual cell counts using IVCM images (ZAS).

Statistical Analysis

Data were collected and tabulated into an Excel spreadsheet for analysis (Microsoft, Inc., Seattle, WA, USA). Where applicable throughout this manuscript, data is reported as mean $\pm$ standard deviation. Pearson's correlation coefficients were used to determine relationships between variables studied. T-tests were used to compare independent means within the data. P-values less than 0.05 were considered to be statistically significant.

Results

Imaging Findings

We identified 154 eyes of 126 patients with FECD that met criteria for inclusion in this study. Eyes were graded from 1 to 4, and imaging from each eye included central and peripheral endothelial photos. Sample central and peripheral endothelial photographs for grade 1 and 3 eyes after cell counts were performed are presented in Figure 2.

Demographic and Follow Up Data

Of the 154 eyes, 74 (48.1%) were the right eye and 80 (51.9%) were the left eye. Of the 126 patients, 82 (65.1%) were female and 44 (34.9%) were male. The mean age at the date of visit was 66.0 $\pm$ 9.4 years (range 46 to 88 years). The mean period of follow up was 29.9 $\pm$ 19.7 months (range 3 to 83 months) from the date of visit.

Data Stratified by Disease Grade

Table 1 presents the average age at date of visit, percent female, and clinical/imaging features after stratifying by disease grade. As shown in Table 1, with increasing disease grade, the age at visit date increased. However, this relationship was not statistically significant, although there was a trend towards statistical significance ($p = 0.054$). Mean disease grade among females was 1.89 $\pm$ 0.75. Mean disease grade among males was 2.16 $\pm$ 0.88. This difference was statistically significant ($p < 0.05$). With higher disease grades, central ECC and peripheral ECC decreased, visual acuity worsened, and CCT increased (Table 1). These correlations were all statistically significant (all $p < 0.05$).

Eyes Requiring Surgery During Follow Up

Forty-one eyes eventually required surgery during follow up. Of these, 26 underwent Descemet membrane endothelial keratoplasty (DMEK), 11 underwent Descemet stripping endothelial keratoplasty (DSEK), 2 underwent Descemet stripping, and 2 underwent penetrating keratoplasty. The percentage of eyes requiring surgery stratified by disease grade is presented in Table 2. As seen in Table 2, higher grades were associated with a larger proportion of eyes eventually undergoing surgery. Furthermore, the time to surgery was lower with more advanced disease grades (Table 2), and this relationship was statistically significant ($p < 0.05$). In addition, the time to surgery showed an inverse correlation with CCT, and this relationship was also significant ($p < 0.05$).

Among females, 17/99 (17.2%) eventually underwent surgery, while among males, 24/55 (43.6%) required surgery during follow up. This difference was statistically significant ($p < 0.05$).

Correlations Between Pairs of Clinical Variables

Table 3 presents the statistical significance of correlations between various pairs of clinical variables. When evaluating central ECC, peripheral ECC, LogMAR BCVA, disease grade, and CCT, each of the 5 variables significantly correlated with each of the other variables (Table 3).

Correlations in Advanced Disease Grades

Among eyes with a disease grade of 3 or 4, clinical correlations are presented in Table 4. Of the 5 variables studied, peripheral ECC had the highest number of statistically significant correlations with other variables (2 statistically significant correlations). Each of the other variables had 1 or 0 statistically significant correlations. Peripheral ECC was the only variable that significantly correlated with central ECC and disease grade (Table 4).

Correlations in Thickened Corneas

Among eyes with CCT > 700, clinical correlations are presented in Table 5. Peripheral ECC demonstrated 3 statistically significant correlations, the highest of the clinical variables studied. Peripheral ECC was the only variable studied that demonstrated a statistically significant relationship with clinical disease grade (Table 5).

Correlations in Cases of Low Central ECC

Among eyes with central ECC < 350, correlations are presented in Table 6. Peripheral ECC had the highest number of statistically significant correlations with other clinical variables. In addition, peripheral ECC was the only feature that significantly correlated with CCT (Table 6).

Peripheral ECC According to Location of Cell Count

Of the 154 eyes included in this study, peripheral ECC measurements were obtained inferiorly in 29 (18.8%) eyes, nasally in 62 (40.2%) eyes, superiorly in 48 (31.2%) eyes, and temporally in 15 (9.7%) eyes. There was no significant difference when comparing values from the superior and inferior peripheral cornea to the nasal and temporal peripheral cornea ($p = 0.859$).

Discussion

In this study, we demonstrate that peripheral ECC is a strong clinical marker of disease severity in advanced FECD, as defined by a high clinical grade, thickened central cornea, or low central ECC. In each of these scenarios, peripheral ECC was the strongest predictor of disease severity as compared to other known markers of FECD progression.

The clinical staging of FECD has been widely explored, and to this day there is no consensus on the best method to grade this condition. While slit lamp grading of the disease is common, agreement between corneal specialists on subjective and morphologic grading in FECD is only moderate.¹⁶ Perhaps the most common subjective measure of disease severity used in FECD is the Krachmer grading system, in which the disease is staged based on slit lamp findings of the confluence and area of guttae in the central corneal zone.⁶

Several objective methods of grading have been developed. The corneal central-to-peripheral thickness ratio is a repeatable, objective measurement that correlates with clinical severity of FECD, and also distinguishes between FECD and normal corneas.¹⁶ Alternatively, effective endothelial cell density (the product of local cell density and the fraction of a confocal image free of guttae) correlates significantly with subjective grade.¹⁷ CCT has also been shown to

correlate directly with FECD severity, although the use of this measure as a substitute for disease grade is limited by the underlying effect of intraocular pressure, age, and contact lens wear on CCT.¹⁸ Finally, the peripheral guttae ratio may be useful for distinguishing advanced grades of FECD and is another potential method of grading.¹² The current findings suggest that peripheral ECC is a promising imaging-based objective measure of disease severity in advanced cases.

Peripheral ECC demonstrated stronger and more correlations with disease severity compared to other disease markers (central ECC, BCVA, clinical disease grade, and CCT). The latter 4 features may be limited in their utility in advanced FECD for a number of reasons. In severe cases of FECD, the central and paracentral endothelia are nearly completely covered by guttae,¹² with peripheral endothelial changes occurring later.⁷ As such, central ECC loses its utility as a metric for disease grade in moderate to advanced FECD, as ECC in the central and paracentral zones would not differ across grades. The earlier central degeneration and disorganization of endothelial cells may be secondary to the high density of regenerative endothelial precursor cells in the peripheral cornea.^{19,20} BCVA may be limited as a marker for disease severity in FECD due to the effect of coexisting cataract or retinal pathology. Clinical grading of FECD is limited by its subjectivity, with moderate agreement across specialists.¹⁶ Finally, CCT may be limited because with early central endothelial damage, the central cornea swells primarily and the peripheral cornea remains relatively unaffected until the final stages of FECD.²¹ Given that central corneal endothelial cells are essentially obliterated in advanced FECD, the cornea may reach its maximum point of swelling before the final stages of FECD.²²

Interestingly, our findings demonstrated a higher average disease grade in males compared to females, with a higher percentage of males eventually undergoing corneal surgery. These findings parallel those reported in a study by Afshari et al., which found that men were an average of 4 years younger than women at the time of corneal transplant for FECD, and that preoperative corneal thickness was slightly greater in men.²³ To the best of our knowledge, there is no known pathophysiologic mechanism for more rapid FECD progression in men compared to women. The gender disparity identified in our study may be due to the characteristic of men to often present with later ocular disease than women, and this trend has been previously demonstrated in the case of glaucoma.²⁴

The value of IVCN in the diagnosis and evaluation of FECD has been previously described.^{25–27} Scanning slit IVCN has been shown to detect changes in the basal epithelium, Bowman's layer, anterior stroma, posterior stroma, Descemet membrane, and endothelium in FECD.²⁵ Furthermore, the ECC obtained by IVCN correlates strongly with counts obtained by standard specular microscopy.²⁵ IVCN has been proposed as an effective means to study the corneal stroma in cases of FECD in which it may appear clinically normal but has perhaps undergone subclinical changes.²⁷ In this regard, it may have a role in preoperative evaluation and in evaluating the response of the corneal stroma to endothelial keratoplasty.²⁷

In advanced cases of FECD, keratoplasty remains the mainstay of treatment. While penetrating keratoplasty was once the leading surgical treatment for FECD, DSEK and

DMEK have emerged as the primary methods of treatment.^{28–33} Descemet stripping without endothelial keratoplasty was recently identified as a potential technique in the management of FECD, although further research is needed to understand its clinical applicability.³⁴ In our study, the percentage of eyes requiring surgical treatment for FECD increased with higher disease grades, an expected correlation given the effect of advanced FECD on visual acuity. Furthermore, the time to surgery inversely correlated with disease grade, with stage 1, stage 2, stage 3, and stage 4 disease eyes undergoing surgery an average of 30.8 months, 15.0 months, 9.2 months, and 2.5 months later, respectively. These findings may be useful in educating patients about the natural course of their disease, and may guide clinical follow up intervals.

Several weaknesses to this study have been noted. First, we did not measure the exact distance of peripheral ECC measurements from the central axis, and the location of peripheral images may have varied across eyes. However, all images were obtained by one of two technicians, both of whom practiced very similar techniques. Furthermore, the large number of eyes included in this study likely would minimize the effect of differences due to small displacements in the location of measurements. Second, we obtained a single peripheral ECC in each eye. It has been shown that the inferotemporal cornea is often the most severely damaged area in FECD, possibly due to a lack of protection by the eyelid and nose from ultraviolet light.^{35,36} Furthermore, we know that guttae tend to spread more horizontally than vertically.³⁷ Thus, the location of the peripheral photograph may have affected the ECC. However, as demonstrated in our results, there was no significant difference between the superior and inferior peripheral cornea and the nasal and temporal peripheral cornea ($p = 0.859$). Third, LogMAR BCVA was used as a measure of disease severity in our study, but the study did not account for decreases in visual potential due to cataract or posterior pathology. For this reason, we used multiple measures of disease severity to allow for a broader picture of disease progression. Finally, although it is important to note age-related changes in central and peripheral ECC, which could have thus affected our results, we did not find a statistically significant relationship between grade and age. In addition to the large number of eyes studied in this report, strengths of this study include a single cornea specialist performing all slit lamp exams (allowing for consistent grading), and the use of two investigators for chart reviews (reducing potential observer bias).

In conclusion, in cases of advanced FECD, severity is best determined by peripheral ECC as compared to central ECC, BCVA, clinical disease grade, and CCT. Peripheral ECC may be an objective imaging-based marker to monitor FECD progression in severe cases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of public and private financial support to disclose: None

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Figure 1.

Endothelial image from a healthy eye taken using Heidelberg Retina Tomograph (HRT) 3. A region of interest (ROI) with a minimum area of 0.03 mm² was defined and the number of cells within the ROI was manually counted, resulting in a cellular density value.

Figure 2. Sample central and peripheral endothelial photographs after manual cell counts have been performed. A: Central endothelium from grade 1 eye. B: Peripheral endothelium from grade 1 eye. C: Central endothelium from grade 3 eye. D: Peripheral endothelium from grade 3 eye.

Variables According to Disease Grade; ECC = endothelial cell count; LogMAR = logarithm of the minimum angle of resolution; BCVA = best corrected visual acuity; CCT = central corneal thickness

Table 1

	Age at visit date	Percent female	Central ECC	Peripheral ECC	LogMAR BCVA	CCT
Grade 1	64.8 +/- 9.8 years	68.8%	1392 +/- 591	1770 +/- 501	0.114 +/- 0.162	585 +/- 44
Grade 2	65.6 +/- 9.1 years	70.0%	668 +/- 382	1338 +/- 352	0.209 +/- 0.152	626 +/- 43
Grade 3	68.2 +/- 9.6 years	46.9%	442 +/- 257	831 +/- 265	0.432 +/- 0.303	673 +/- 69
Grade 4	70.5 +/- 5.8 years	50.0%	205 +/- 91	387 +/- 202	0.619 +/- 0.506	733 +/- 116

Table 2

Requirement for Surgery According to Disease Grade

	Eyes requiring surgery	Time to surgery (months)
Grade 1	5/48 (10.4%)	30.8 +/- 14.6
Grade 2	8/70 (11.4%)	15.0 +/- 11.3
Grade 3	24/32 (75.0%)	9.2 +/- 10.9
Grade 4	4/4 (100.0%)	2.5 +/- 1.0

Table 3

Correlations Between Pairs of Clinical Variables; ECC = endothelial cell count; LogMAR = logarithm of the minimum angle of resolution; BCVA = best corrected visual acuity; CCT = central corneal thickness

	Peripheral ECC	LogMAR BCVA	Grade	CCT
Central ECC	p < 0.05	p < 0.05	p < 0.05	p < 0.05
Peripheral ECC		p < 0.05	p < 0.05	p < 0.05
LogMAR BCVA			p < 0.05	p < 0.05
Grade				p < 0.05

Table 4

Correlations Among Eyes with Grade 3 or 4 Disease; ECC = endothelial cell count; LogMAR = logarithm of the minimum angle of resolution; BCVA = best corrected visual acuity; CCT = central corneal thickness

	Central ECC	Peripheral ECC	LogMAR BCVA	Grade	CCT
Central ECC		$p < 0.05$	$p > 0.10$	$p = 0.090$	$p > 0.10$
Peripheral ECC	$p < 0.05$		$p > 0.10$	$p < 0.05$	$p > 0.10$
LogMAR BCVA	$p > 0.10$	$p > 0.10$		$p > 0.10$	$p > 0.10$
Grade	$p = 0.089$	$p < 0.05$	$p > 0.10$		$p > 0.10$
CCT	$p > 0.10$	$p = 0.063$	$p > 0.10$	$p > 0.10$	

Table 5

Correlations Among Eyes with CCT > 700; ECC = endothelial cell count; LogMAR = logarithm of the minimum angle of resolution; BCVA = best corrected visual acuity; CCT = central corneal thickness

	Central ECC	Peripheral ECC	LogMAR BCVA	Grade	CCT
Central ECC		$p < 0.05$	$p > 0.10$	$p > 0.10$	$p < 0.05$
Peripheral ECC	$p < 0.05$		$p > 0.10$	$p < 0.05$	$p < 0.05$
LogMAR BCVA	$p > 0.10$	$p > 0.10$		$p > 0.10$	$p > 0.10$
Grade	$p > 0.10$	$p < 0.05$	$p > 0.10$		$p = 0.096$
CCT	$p < 0.05$	$p < 0.05$	$p > 0.10$	$p = 0.096$	

Table 6

Correlations Among Eyes with Central ECC < 350; ECC = endothelial cell count; LogMAR = logarithm of the minimum angle of resolution; BCVA = best corrected visual acuity; CCT = central corneal thickness

	Central ECC	Peripheral ECC	LogMAR BCVA	Grade	CCT
Central ECC		p > 0.10	p > 0.10	p > 0.10	p > 0.10
Peripheral ECC	p > 0.10		p < 0.05	p < 0.05	p < 0.05
LogMAR BCVA	p > 0.10	p < 0.05		p < 0.05	p > 0.10
Grade	p > 0.10	p < 0.05	p < 0.05		p = 0.071
CCT	p > 0.10	p < 0.05	p > 0.10	p = 0.071	