Original Article

Diurnal changes of corneal epithelial and stromal thickness maps and visual quality in mild form of Fuchs' endothelial corneal dystrophy

Iva Krolo[1,2,3], Aida Kasumović Bećirević[1,4], Ivana Radman[1], Armin Kasumović[1], Ines Matoc[1], Idoia Goñi Guarro[1], Ivan Sabol[5]

Purpose: To investigate the functional and structural daily variations in eyes with a mild form of Fuchs' endothelial corneal dystrophy (FECD). **Methods:** This prospective study included 30 eyes with the mild form of FECD. Subjects underwent functional and structural testing at 8 AM, 2 PM, and 8 PM. Testing included measurement of uncorrected distance visual acuity (UDVA), best corrected twilight vision (TV), and contrast sensitivity function (CSF) testing (Vista Vision Far-Pola, DMD MedTech charts). Corneal epithelial and stromal parameters were evaluated with anterior segment optical coherence tomography (AngioVue, AvantiRTVue-XR; Optovue, CA, USA). **Results:** UDVA, TV, and CSF for spatial frequencies B, C, and F showed significant changes during the day, with the lowest values in the morning ($P < 0.0001$ for UDVA, $P = 0.0109$ for TV, and $P < 0.0001$, $P = 0.0126$, and $P = 0.0471$ for the three spatial frequencies, respectively). There was no significant change in epithelial parameters between visits. Central corneal thickness showed significant decrease during the day ($P < 0.0001$), as did the central stromal thickness on the 5- and 7-mm maps ($P = 0.0002$ and $P < 0.0001$, respectively), stromal thickness in the superior section of the 5-mm map ($P = 0.0107$), stromal thickness in the inferior section of the 7-mm map ($P = 0.0002$), and minimal stromal thickness on both maps ($P < 0.0001$). **Conclusion:** A significant negative correlation was found between central stromal thickness and TV, implying that simultaneous evaluation of corneal layers and visual quality may be useful in assessing FECD.

Key words: Anterior segment optical coherence tomography, epithelial corneal maps, Fuchs' corneal dystrophy, stromal corneal maps, visual quality

Access this article online

Website: https://journals.lww.com/ijo

DOI: 10.4103/IJO.IJO_282_24

Quick Response Code:

Fuchs' endothelial corneal dystrophy (FECD) affects the corneal endothelium and can lead to bilateral corneal edema causing significant visual disturbances.[1-5] There is also a significant diurnal variation of corneal thickness, with impaired visual quality in the morning and improvement during the day.[6-10]

A commercially available tool for Avanti RTVue XR (Optovue, Inc., Fremont, CA, USA) allows mapping of the cornea, including separate quantitative evaluation of the epithelial and stromal layers.[11,12]

In this study, we performed a diurnal analysis of functional (visual quality) and structural corneal (epithelial and stromal thickness) changes in eyes with the mild form of FECD and investigated their correlation.

Methods

Thirty eyes of 30 patients with the mild form of FECD were included in this prospective longitudinal study. Patients were recruited at a tertiary eye care center. After obtaining detailed information, an informed consent form was signed by all subjects. This study followed the tenets of the Declaration of Helsinki, and all experimental protocols were approved by the hospital's ethics committee.

The mild form of FECD was confirmed with the slit-lamp examination, using a modification of the Krachmer grading system, based on the area and confluence of guttae, without the presence of corneal edema. The modified Krachmer FECD grading scale has been used to subjectively evaluate disease progression as follows: grade 0, no guttae; grade 1, up to 12 scattered central guttae; grade 2, 12 or more scattered central guttae; grade 3, 1–2 mm of confluent central guttae; grade 4, 2–5 mm of confluent central guttae; grade 5, greater than 5 mm confluent central guttae without stromal edema; and

[1]University Department of Ophthalmology, University Hospital Center Sestre Milosrdnice, Vinogradska Cesta 29, Zagreb, Croatia, [2]Department of Medicine and Pharmacology, Vrije Universiteit Brussel (VUB), Bd de la Plaine 2, Brussels, Belgium, [3]Oftalmología Médica y Quirúrgica (OMIQ) Research, Servicio de Oftalmología, C/de Londres, 38, 1° Planta, Eixample, Barcelona, Spain, [4]Department of Ophthalmology, Eye Polyclinic Dr. Sefić, Ferhadija 5, Sarajevo, Bosnia and Herzegovina, [5]Department of Molecular Medicine, Ruđer Bošković Institute, Bijenicka Cesta 54, Zagreb, Croatia

Correspondence to: Dr. Aida Kasumović Bećirević, University Department of Ophthalmology, University Hospital Center Sestre Milosrdnice, Vinogradska Cesta 29, 10000 Zagreb, Croatia. E-mail: aidakasumovic1@hotmail.com

Received: 30-Jan-2024 Revision: 15-Jun-2024
Accepted: 24-Jul-2024 Published: 10-Sep-2024

Cite this article as: Krolo I, Kasumović Bećirević A, Radman I, Kasumović A, Matoc I, Goñi Guarro I, *et al*. Diurnal changes of corneal epithelial and stromal thickness maps and visual quality in mild form of Fuchs' endothelial corneal dystrophy. Indian J Ophthalmol 2025;73:122-7.

grade 6, greater than 5 mm confluent central guttae with stromal edema.[13] Endothelial cell density, hexagonality, and coefficient of variation were measured with an endothelial specular microscope (EM-4000; Tomey, Nuremberg, Germany) on the first visit [Fig. 1]. Exclusion criteria included any signs of clinical corneal edema observed on the slit lamp, previous eye surgery or contact lens wear, ocular hypertension and other pathology affecting the cornea, lens, and retina. None of the patients had diabetes mellitus, or any other systemic disease, and had not used systemic or topical medications known to affect the cornea. If both eyes of one patient were eligible for inclusion, only the right eye was monitored.

All patients underwent functional and structural testing three times during the day: at 8 AM (approximately 1 h after waking up), at 2 PM, and at 8 PM. Visual function testing included the measurement of uncorrected distance visual acuity (UDVA), best corrected twilight vision (TV), and contrast sensitivity function (CSF) testing (Vista Vision Far Pola; DMD MedTech charts, Torino, Italy). UDVA was tested monocularly using Early Treatment Diabetic Retinopathy Study charts at a 4-m distance under photopic (100 cd/m^2) normal room lighting conditions.

As for the visual quality, CSF was measured with "FAST 2-1" psycho-physic procedure (Vista Vision Far-Pola; DMD MedTech charts, Italy). This is a commercially available contrast sensitivity measurement tool with good reliability that applies sinusoidal gratings. It uses a subjective method of forced-choice detection and measures the contrast sensitivity at six levels of spatial frequencies (SFs): 0.75, 1.5, 3, 6, 12, and 18 cycles per degree (cpd). Each set of SF contains sinusoidal grating patches of eight contrast sensitivities, starting with the highest value and with progressively decreasing contrast strength. Each sinusoidal grating patch contained a bar with the brightest and darkest luminance, with the thickness of the bar depending on SF of the grating. The contrast sensitivity value of the last correct response in each SF was documented. This data allows the CSF to be drawn as a graph report, where the area under the resulting curve describes the total visual "space" that can be perceived. Better spatial vision is represented by a larger area under the CSF curve. CSF was tested under photopic lighting. Patients stood 3 m away from the chart, with their heads leveled with the screen.

TV was measured using a commercially available validated computerized mesopic VA test (Vista Vision Far-Pola; DMD MedTech charts, Italy). The illumination of the environment was obscured to 1 lux. The test showed one line of letters with a light background of 1 cd/m^2, as specified by the manufacturer. Each row consisted of five Sloan optotypes with values of visual acuity ranging from 0.1 to 1.0. The subjects were allowed 5 min of adaptation to ambient light conditions before the test, after which they were asked to read black letters on a dim screen plane. Visual acuity was verified starting from the first line of the optotype. Both the visual acuity and TV tests were scored letter by letter, with a termination rule of stopping after three or more mistakes within a single line.

Daily structural changes in patients with FECD included measurement of corneal epithelial and stromal parameters using anterior segment optical coherence tomography (AS-OCT; AngioVue, AvantiRTVue-XR; Optovue, Fremont, CA, USA). The evaluated parameters included central epithelial thickness (CET), epithelial thickness in the superior section of the map (S_e), epithelial thickness in the inferior section of the map (I_e), difference in epithelial thickness between the superior and inferior sections of the map ($S - I_e$), minimal epithelial thickness (Min_e), maximal epithelial thickness (Max_e), and central corneal thickness (CCT). The evaluated stromal parameters included central stromal thickness (CST), stromal thickness in the superior section of the map (S_s), stromal thickness in the inferior section of the map (I_s), difference in stromal thickness between the superior and inferior sections of the map (S – Is), as well as minimal stromal thickness (Min_s) and maximal stromal thickness (Max_s). All parameters were analyzed on pachymetry (P) and pachymetry wide maps, which scanned and measured 6 and 9 mm of the cornea in diameter, respectively.

The data were entered into Microsoft Excel tables and analyzed using MedCalc (v20.111; MedCalc software, Ostend,

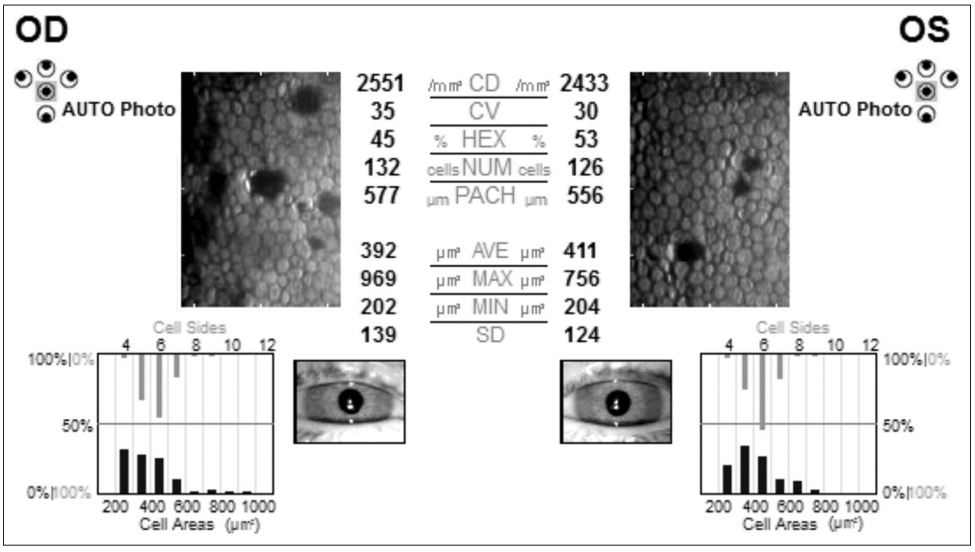


Figure 1: Endothelial specular microscopy scan in the mild form of Fuchs' endothelial corneal dystrophy. Note the presence of nonconfluent guttae, with normal endothelial cell density

Belgium). Since every participant was fully examined, there were no missing values; each calculation was done on a total of 30 observations. Normality of the distribution of numeric variables was assessed using the Kolmogorov–Smirnov test. Depending on normality, the differences between 8 AM, 2 PM, and 8 PM measurements were analyzed with repeated measures analysis of variance (ANOVA) for normally distributed variables or with Friedman test (nonparametric repeated measures ANOVA) for non-normally distributed variables. Correlations between two variables were assessed using Spearman rank correlation coefficient at each timepoint separately. Apparently significant correlations were validated with repeated measures correlation calculated with "rmcorr" package (v0.6.0) in R (v 4.2.2).[14] *P* values < 0.05 were considered significant.

Results

Thirty eyes of 30 patients were recruited for this study, 43% of whom were male. Their mean age was 56.6 ± 10.5 years. Of these eyes, 53% were classified as grade 1 and 47% as grade 2 of the modified Krachmer grading system. The mean endothelial cell density on the first visit was 2087.8 ± 537.7 cells/mm^2, hexagonality value was 40.3% ± 9.6%, and coefficient of variation was 44.5% ± 8.5%.

Regarding visual function, UDVA and TV showed significant changes during the day [Table 1]. UDVA was the lowest in the morning (0.46 ± 0.31 Snellen line) and showed gradual improvement during the day, measuring 0.53 ± 0.34 Snellen line in the evening ($P < 0.0001$). However, TV showed the highest result at 2 PM (0.82 ± 0.17, $P = 0.0109$). CSF showed a similar pattern [Table 1]. The results for all SFs were the lowest at the 8 AM visit and improved during the day. Significant changes during the day were observed for the SFs B, C, and F ($P < 0.0001$, $P = 0.0126$, and $P = 0.0471$, respectively).

CCT measured by AS-OCT showed significant changes during the day, with the highest values in the morning and lowest in the evening (547.09 ± 32.04 and 542.69 ± 31.59, respectively, $P < 0.0001$). There was no significant change in CET or other epithelial parameters between the visits, except for the S value on the 7-mm map ($P = 0.0466$). CCT and epithelial parameters are listed in Table 2.

Regarding corneal stroma, significant diurnal changes were confirmed for CST on both 5- and 7-mm maps ($P = 0.0002$ and $P < 0.0001$, respectively), stromal thickness in the superior section of the 5-mm map ($P = 0.0107$), stromal thickness in the inferior section of the 7-mm map ($P = 0.0002$), and minimal stromal thickness on both 5- and 7-mm maps ($P < 0.0001$ for both parameters). The diurnal values of corneal stromal parameters are shown in Table 3.

As seen in Table 4, a significant negative correlation was noted between TV and CST on both 5- and 7-mm maps at all three visits during the day. Correlation of TV with CST on both maps was also found to be significant when assessed by repeated measures correlation [Table 4 and Supplementary Fig. 1].

Discussion

Extensive studies have been performed to better understand the most common corneal dystrophy and improve its management in everyday clinical practice. It has been widely reported that FECD is characterized by a gradual loss of endothelial cells, which can lead to various degrees of epithelial and/or stromal edema, resulting in loss of vision, painful bullous keratopathy, and chronic loss of corneal transparency.[3] However, anterior corneal cellular and structural abnormalities begin early in the course of Fuchs' dystrophy, before the appearance of clinically evident edema.[9] Previous studies have compared the corneal thickness measurements at different times of the day in patients with varying degrees of disease severity.[15] A study published by Fritz *et al*.[8] analyzed if patients with advanced FECD had a thicker cornea in the morning than in the late afternoon. A noticeable degree of morning edema was found upon awakening in those corneas, which resolved within the first 4 h after eye opening. The development of new surgical techniques, mainly Descemet stripping only (DSO), and also Descemet membrane transplantation and cell-based therapy, bypasses the difficulties surrounding keratoplasty procedures dependent on donor corneal tissue and removes the risks associated with graft rejection and failure. In addition, it enables us to maintain close-to-optimal function of mild FECD corneas for a prolonged period of time.[16] There are still many unknowns surrounding the DSO procedure, including determining the right time for surgical treatment and prediction

Table 1: Diurnal measurements of visual acuity, TV, and CS function in patients with the mild form of Fuchs' endothelial corneal dystrophy (*n*=30)

Vision parameters	Time			
	8 AM	2 PM	8 PM	*P*[a]
UDVA (decimal; mean±SD)	0.46±0.31	0.50±0.31	0.53±0.34	**<0.0001**
TV (decimal; mean±SD)	0.78±0.20	0.82±0.17	0.80±0.17	**0.0109**
CS spatial frequency A (CS level; mean±SD)	6.00±1.11	6.20±0.84	6.2±1.56	0.0879
CS spatial frequency B (CS level; mean±SD)	6.80±0.92	7.43±0.72	7.26±1.11	**<0.0001**
CS spatial frequency C (CS level; mean±SD)	7.00±0.90	7.50±0.62	7.36±0.99	**0.0126**
CS spatial frequency D (CS level; mean±SD)	6.26±1.57	6.43±1.22	6.50±1.16	0.4388
CS spatial frequency E (CS level; mean±SD)	4.33±1.44	4.76±1.56	4.83±1.66	0.1205
CS spatial frequency F (CS level; mean±SD)	2.60±1.75	3.00±1.59	3.16±2.13	**0.0471**

Significant values are highlighted in bold, A=spatial frequency of 0.75 cycles per degree (cpd), B=spatial frequency of 1.50 cycles per degree (cpd), C=spatial frequency of 3 cycles per degree (cpd), CS=contrast sensitivity, D=spatial frequency of 6 cycles per degree (cpd), E=spatial frequency of 12 cycles per degree (cpd), F=spatial frequency of 18 cycles per degree (cpd), SD=standard deviation, TV=twilight vision, UDVA=uncorrected distance visual acuity. [a]Friedman test *P*

Table 2: Diurnal measurements of epithelial parameters using epithelial mapping on anterior segment optical coherent tomography (*n*=30)

Epithelial parameters (μm; mean±SD)	Time			
	8 AM	2 PM	8 PM	*P*
CET on 5-mm map	53.39±4.68	52.61±4.52	54.23±4.51	0.2577[a]
CET on 7-mm map	53.21±4.55	53.41±3.29	54.41±4.57	0.2150[a]
S_e on 5-mm map	50.57±4.85	50.16±4.38	51.78±4.83	0.4411[a]
S_e on 7-mm map	49.38±5.26	49.60±2.76	50.50±4.20	**0.0466[a]**
I_e on 5-mm map	53.43±4.71	52.86±4.61	54.67±4.64	0.0574[a]
I_e on 7-mm map	52.69±4.30	53.01±3.17	53.75±3.92	0.2720[a]
S - I_e on 5-mm map	-2.76±1.80	-2.76±1.94	-2.90±2.05	0.7900[b]
S - I_e on 7-mm map	-3.24±2.26	-3.40±2.12	-3.53±2.86	0.7770[b]
Min_e on 5-mm map	47.68±4.61	47.02±4.31	48.75±4.56	0.2648[a]
Min_e on 7-mm map	44.04±8.50	45.35±3.74	45.70±3.60	0.6033[a]
Max_e on 5-mm map	55.89±5.35	54.99±5.13	57.02±5.26	0.5671[a]
Max_e on 7-mm map	56.70±4.74	57.43±3.61	57.83±4.89	0.8221[a]
CCT on AS-OCT	547.09±32.04	542.70±31.64	542.69±31.59	**<0.0001[a]**

Significant values are highlighted in bold, ANOVA=analysis of variance, CCT=central corneal thickness, CET=central epithelial thickness, I_e=epithelial thickness in the inferior section of the map, Max_e=maximal epithelial thickness, Min_e=minimal epithelial thickness, SD=standard deviation, S_e=epithelial thickness in the superior section of the map, S - I_e=the difference in epithelial thickness between the superior and inferior sections of the map. [a]Friedman test. [b]Repeated measures ANOVA test

Table 3: Diurnal measurements of stromal parameters using stromal mapping on anterior segment optical coherent tomography (*n*=30)

Stromal parameters (μm; mean±SD)	Time			
	8 AM	2 PM	8 PM	*P*
CST on 5-mm map	492.80±31.61	490.78±30.26	488.87±31.00	**0.0002[a]**
CST on 7-mm map	494.38±30.34	491.21±34.17	487.70±31.01	**<0.0001[a]**
S_s on 5-mm map	524.63±32.45	520.06±32.09	519.50±34.27	**0.0107[a]**
S_s on 7-mm map	555.38±35.16	553.11±35.34	551.68±33.27	0.4923[a]
I_s on 5-mm map	510.23±34.17	509.56±34.55	507.83±34.31	0.5740[b]
I_s on 7-mm map	536.62±33.49	533.21±33.29	528.81±31.77	**0.0002[b]**
S - I_s on 5-mm map	14.40±16.39	10.50±22.18	11.66±16.44	0.4210[b]
S - I_s on 7-mm map	18.76±24.13	19.89±21.11	22.87±15.95	0.5042[b]
Min_s on 5-mm map	486.33±32.17	483.70±31.44	481.56±31.77	**<0.0001[a]**
Min_s on 7-mm map	486.66±31.55	482.50±31.01	481.56±31.08	**<0.0001[a]**
Max_s on 5-mm map	546.66±31.17	547.83±30.51	543.96±31.16	0.6168[a]
Max_s on 7-mm map	601.50±33.69	598.86±36.97	595.83±33.73	0.0930[a]

Significant values are highlighted in bold, ANOVA=analysis of variance, CST=central stromal thickness, I_s – stromal thickness in the inferior section of the map, Max_s=maximal stromal thickness, Min_s=minimal stromal thickness, SD=standard deviation, S_s=stromal thickness in the superior section of the map, S - I_s=the difference in stromal thickness between the superior and inferior sections of the map. [a]Friedman test. [b]Repeated measures ANOVA test

of its success.[17] Understanding the corneal structural changes and correlating them to functional loss may be of great importance in developing a reliable algorithm for the DSO treatment and its postoperative follow-up.

Despite the primary pathologic process in Fuchs' dystrophy occurring at the level of corneal endothelium, the effects of corneal guttata result in an increased degree of backscatter in the entire corneal thickness.[18] FECD certainly affects visual acuity, but one of the earliest symptoms is glare, caused by light scatter from the guttae and corneal edema.[6,19-21] Patients with a higher degree of corneal remodeling of the posterior surface have worse diurnal variations and glare-related disabilities that concomitantly increase the visual acuity-related disturbances.[19] In our study, visual performance was tested three times during the day. The results coincide with those obtained in previously published articles, given that uncorrected visual acuity, CSF, and TV showed the lowest values at the morning visit, with a gradual improvement during the day.[8,9,22] A remarkable difference of this study is the method of contrast sensitivity evaluation, which was tested for six SFs, as well as TV testing, which represents a very thorough and detailed analysis of the visual quality.

In recent years, AS-OCT, ultrasonic biomicroscopy, as well as Scheimpflug tomography have been incorporated for a more in-depth analysis of patients with FECD.[23] Qualitative AS-OCT characteristics of FECD have been described in previous case series.[24,25] The device was used to analyze the optical density of the cornea, which significantly expanded the knowledge about its structure, especially of the anterior subepithelial stromal region, where subepithelial fibrosis and scarring can occur.[26] Corneal thickening was believed to occur mainly in the later

Table 4: Correlation of CST on 5- and 7-mm map with visual function and quality parameters (*n*=30)[a]

Vision parameters		CST 5-mm map				CST 7-mm map			
		Time			Repeated measures	Time			Repeated measures
		8 AM	2 PM	8 PM		8 AM	2 PM	8 PM	
UDVA	*R*	-0.16	-0.06	-0.05	-0.09	-0.14	-0.03	-0.03	-0.05
	P	0.3834	0.7234	0.7844	0.4	0.4559	0.876	0.8678	0.66
TV	*r*	-0.65	-0.68	-0.63	-0.63	-0.64	-0.58	-0.63	-0.55
	P	**0.0001**	**<0.0001**	**0.0002**	**<0.001**	**0.0001**	**0.0006**	**0.0002**	**<0.001**
CS spatial frequency B	*r*	-0.36	-0.04	-0.13	-0.16	-0.38	0.00	-0.09	-0.10
	P	0.0537	0.8376	0.5053	0.15	0.0406	1.000	0.6426	0.36
CS spatial frequency C	*r*	-0.31	-0.25	-0.19	-0.14	-0.31	-0.21	-0.12	-0.09
	P	0.0906	0.1881	0.3282	0.2	0.1003	0.2712	0.5449	0.41
CS spatial frequency F	*r*	-0.45	-0.33	-0.39	-0.36	-0.48	-0.26	-0.39	-0.31
	P	**0.0133**	0.0746	**0.0310**	**<0.001**	**0.0072**	0.1736	**0.0339**	**<0.01**

Significant values are highlighted in bold, B=spatial frequency of 1.50 cycles per degree (cpd), C=spatial frequency of 3 cycles per degree (cpd), CS=contrast sensitivity, CST=central stromal thickness, F=spatial frequency of 18 cycles per degree (cpd), TV=twilight vision, UDVA=uncorrected distance visual acuity, *P*=probability value, *r*=correlation coefficient. [a]Individual timepoint correlation was assessed by Spearman correlation and confirmed by repeated measures correlation (rmcorr package) in *R*

stages of FECD, manifesting as clinically apparent stromal and/or epithelial edema.[3,5] Studies have suggested that there is a gradual increase in CCT as FECD progresses, showing higher values in the first hours upon awakening in advanced forms of FECD and progressive thinning during the day, which has been associated with hypoxic swelling from overnight eyelid closure.[8] Our study showed the same pattern of CCT change during the day, confirming it is present even in a mild form of FECD. However, because this change was not greater than 10 μm, it may not have major clinical significance. Moreover, a recent retrospective study by Guindolet *et al*.[27] concluded that there were local changes in corneal thickness in patients with FECD who underwent cataract surgery. Several studies have postulated that CCT is an indicator of corneal endothelial function.[28,29] However, as shown in this study, CCT should not be taken as an isolated measurement of corneal thickness in mild forms of Fuchs' dystrophy due to the difficulty in distinguishing corneas with subclinical edema and naturally thicker corneas (without any edema).[15,30] Therefore, evaluation of CCT variation patterns with other complementary data in eyes with FECD is recommended, rather than relying on a specific cut-off for CCT.[28,29]

AS-OCT software also allows quantitative imaging of the corneal epithelium and stroma independently in the form of maps, which were used in this study to evaluate the diurnal change of the two corneal layers in the mild form of FECD. So far, individual corneal layers in FECD have been explored less extensively than CCT. Reinstein *et al*.[31] reported that the mean epithelial thickness at the corneal vertex was 53.4 ± 4.6 μm in normal subjects, and that it was greater in the inferior quadrant, while the mean stromal thickness at the corneal vertex was 465.4 ± 36.9 μm.[32] The thickness of the epithelial parameters in our study corresponds to the values obtained in normal subjects, while the stromal parameters showed thicker values at all three visits compared to the reported normal values. Many other studies have shown the use of epithelial and stromal mapping in other corneal pathologies, such as in keratoconus, dry eye disease, following corneal refractive surgery, or in corneal collagen cross-linking, with the aim of evaluating their impact on corneal structure.[33-36] However, corneal epithelium thickness mapping has been used so far only for the evaluation of one corneal dystrophy, epithelial basement membrane dystrophy, where the thicker corneal epithelium in the central and inferior corneal regions has been demonstrated.[37] The epithelium does not always have a homogeneous thickness over the cornea, since it has been postulated that it tends to compensate for the stromal irregularities, or change in relation to corneal edema, as in FECD.[38] Our study was the first to report the diurnal behavior of corneal stroma in mild forms of FECD in nontreated eyes. A significant change during the day was shown for CST and stromal thickness in the inferior and superior sections of the cornea, as well as for the minimal stromal thickness, with the highest thickness values in the morning and the lowest in the evening. In addition, when observing the correlation between structural corneal changes and visual performance, a significant negative correlation was found between CST and TV at all three visits during the day, implying a better quality of vision in dusk with decreased CST of the cornea. The epithelium parameters did not show a significant diurnal change. Therefore, the simultaneous evaluation of epithelial and stromal thickness maps may be useful for detecting local changes and have an emerging role in the assessment of FECD in clinical practice and in future clinical trials. The earliest detection of FECD might aid in preoperative planning for cataract and combined ocular procedures, correct intraocular lens (IOL) calculation, as well as in intra- and postoperative risk evaluation. Since there is increasing interest for refractive lens exchange procedure among our patients and the disease is progressive in nature, early diagnosis is an important base for IOL type selection (from monofocal to premium and toric IOLs) at the moment of the surgery. It has been shown that preoperative IOL measurements in patients with FECD should be performed ideally after administration of hyperosmolar eye drops and as late as possible in the course of the day. In addition to the relevance of the posterior corneal surface measurements in normal eyes before the cataract procedure, it has been shown that early FECD detection improves their accuracy.[39]

This study provided insights into the correlation of corneal structural changes and visual function, based only on the mild forms of FECD. In future, it would be interesting to demonstrate these diurnal variations in more severe cases and on a bigger study sample. Another prospect would be to analyze the

impact of a topical treatment with hypertonic agents or surgical procedure options such as keratoplasty and cataract surgery on these diurnal variations. A delay between eye opening and morning clinic-based measurements should also be considered as the limitation of this study. However, all patients had to be examined within 1 h of waking up.

Conclusion

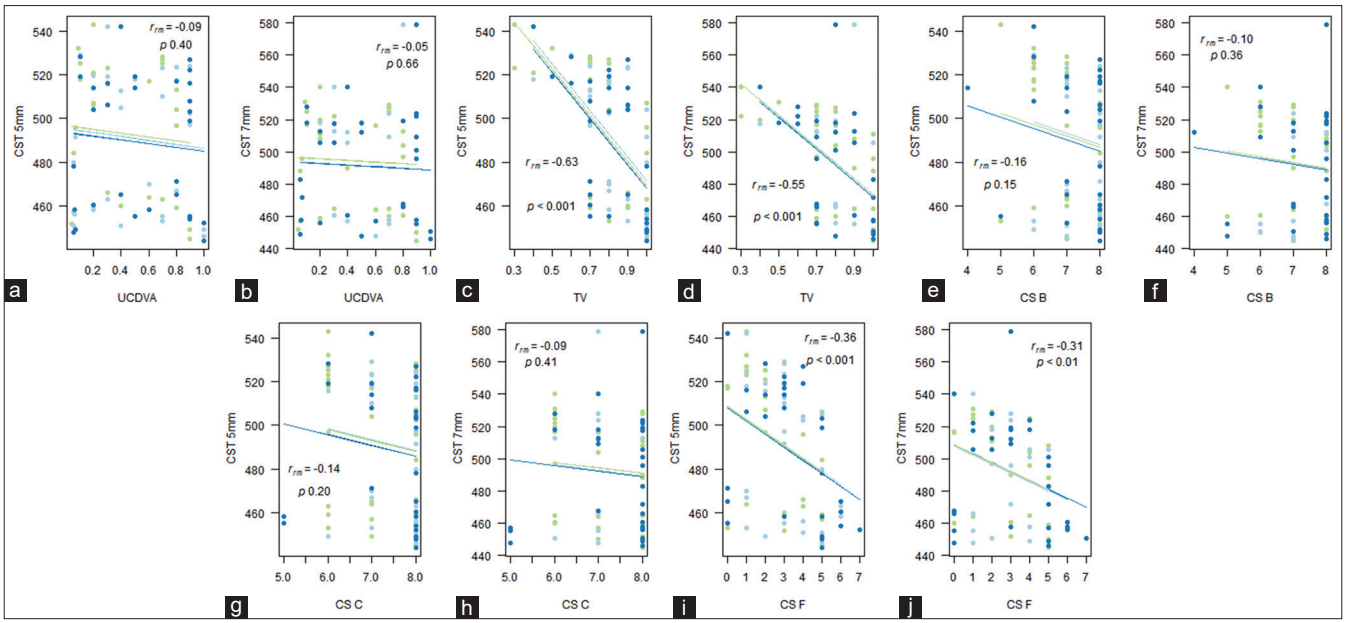
To our knowledge, this is the first prospective study to analyze diurnal variations of epithelial and stromal corneal layers with AS-OCT mapping in patients with a mild form of FECD, correlating structural corneal changes with visual function. According to the results, stromal corneal thickness showed significant diurnal changes in the mild form of FECD, contrary to epithelial thickness, implying subclinical edema formation even in the early stages of the disease. Corneal mapping enables a more precise insight into the behavior of corneal layers, and combining it with visual quality testing may be helpful in monitoring mild FECD patients. This report suggests the importance of multiple daily check-ups in different time periods and the aiding effect of corneal mapping on determining the appropriate time for surgery and postoperative interventions. This paper proposes the inclusion of corneal mapping tools in controlled clinical trials on FECD carried out in future.

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

References

1. Hamill CE, Schmedt T, Jurkunas U. Fuchs endothelial cornea dystrophy: A review of the genetics behind disease development. Semin Ophthalmol 2013;28:281-6.
2. Nanda GG, Alone DP. Review: Current understanding of the pathogenesis of Fuchs' endothelial corneal dystrophy. Mol Vis 2019;25:295-310.
3. Eghrari AO, Gottsch JD. Fuchs' corneal dystrophy. Expert Rev Ophthalmol 2010;5:147-59.
4. Feizi S. Corneal endothelial cell dysfunction: Etiologies and management. Ther Adv Ophthalmol 2018;10:2515841418815802.
5. Oh KT, Weil LJ, Oh DM, Mathers WD. Corneal thickness in Fuchs' dystrophy with and without epithelial oedema. Eye (Lond) 1998;12:282-2849683955.
6. Van der Meulen IJ, Patel SV, Lapid-Gortzak R, Nieuwendaal CP, McLaren JW, van den Berg TJ. Quality of vision in patients with fuchs endothelial dystrophy and after descemet stripping endothelial keratoplasty. Arch Ophthalmol 2011;129:1537-42.
7. Sarnicola C, Farooq AV, Colby K. Fuchs endothelial corneal dystrophy: Update on pathogenesis and future directions. Eye Contact Lens 2019;45:1-10.
8. Fritz M, Grewing V, Maier P, Lapp T, Böhringer D, Reinhard T, *et al*. Diurnal variation in corneal edema in Fuchs endothelial corneal dystrophy. Am J Ophthalmol 2019;207:351-5.
9. Amin SR, Baratz KH, McLaren JW, Patel SV. Corneal abnormalities early in the course of Fuchs' endothelial dystrophy. Ophthalmology 2014;121:2325–33.
10. Okumura N, Padmanaban V, Balaji JJ, Srinivasan B, Hanada N, Komori Y, *et al*. Clinical, morphological, and optical correlates of visual function in patients with fuchs endothelial corneal dystrophy. Cornea 2022;41:171-6.
11. Sridhar MS, Martin R. Anterior segment optical coherence tomography for evaluation of cornea and ocular surface. Indian J Ophthalmol 2018;66:367-72.
12. Hashmani N, Hashmani M, Asghar N, Islam M, Hashmani S. Wide stromal mapping using an anterior segment optical coherence tomography. Clin Ophthalmol 2020;14:751-7.
13. Krachmer JH. Corneal endothelial dystrophy. Arch Ophthalmol 1978;96:2036.
14. Bakdash JZ, Marusich LR. Repeated measures correlation. Front Psychol 2017;8:456.
15. Kopplin LJ, Przepyszny K, Schmotzer B, Rudo K, Babineau DC, Patel SV, *et al*. Relationship of Fuchs endothelial corneal dystrophy severity to central corneal thickness. Arch Ophthalmol 2012;130:433-9.
16. Cheong N, Chui SW, Poon SHL, Wong HL, Shih KC, Chan YK. Emerging treatments for corneal endothelium decompensation-A systematic review. Graefes Arch Clin Exp Ophthalmol 2024;262:381-93.
17. Davies E, Jurkunas U, Pineda R 2nd. Predictive factors for corneal clearance after descemetorhexis without endothelial keratoplasty. Cornea 2018;37:137-40.
18. Ni Dhubhghaill S, Rozema JJ, Tassignon MJ. Corneal Scheimpflug densitometry values measured by pentacam in Fuchs endothelial dystrophy. Invest Ophthalmol Vis Sci 2014;55:2468.
19. Wacker K, Grewing V, Fritz M, Böhringer D, Reinhard T. Morphological and optical determinants of visual disability in Fuchs endothelial corneal dystrophy. Cornea 2020;39:726-31.
20. 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;127:153-60.
21. Patel SV, McLaren JW. *In vivo* confocal microscopy of Fuchs endothelial dystrophy before and after endothelial keratoplasty. JAMA Ophthalmol 2013;131:611-8.
22. Wacker K, Baratz KH, Fautsch MP, Patel SV. Medical and semi-surgical treatments for Fuchs endothelial corneal dystrophy. Klin Monbl Augenheilkd 2018;235:709-13.
23. Ong Tone S, Jurkunas U. Imaging the corneal endothelium in Fuchs corneal endothelial dystrophy. Semin Ophthalmol 2019;34:340-6.
24. Kaluzny BJ, Szkulmowska A, Szkulmowski M, Bajraszewski T, Kowalczyk A, Wojtkowski M. Fuchs' endothelial dystrophy in 830-nm spectral domain optical coherence tomography. Ophthalmic Surg Lasers Imaging 2009;40:198–200.
25. Shousha MA, Perez VL, Wang J, Ide T, Jiao S, Chen Q, *et al*. Use of ultra-high-resolution optical coherence tomography to detect *in vivo* characteristics of Descemet's membrane in Fuchs' dystrophy. Ophthalmology 2010;117:1220-7.
26. Adamis AP, Filatov V, Tripathi BJ, Tripathi RC. Fuchs' endothelial dystrophy of the cornea. Surv Ophthalmol 1993;38:149-68.
27. Guindolet D, Gemahling A, Azar G, Disegni H, Samie M, Cochereau I, *et al*. Detecting subclinical corneal edema using corneal thickness mapping in patients presenting Fuchs endothelial corneal dystrophy. Am J Ophthalmol 2023;246:58-65.
28. Seitzman GD, Gottsch JD, Stark WJ. Cataract surgery in patients with Fuchs' corneal dystrophy: Expanding recommendations for cataract surgery without simultaneous keratoplasty. Ophthalmology 2005;112:441-6.
29. Olson RJ, Braga-Mele R, Chen SH, Miller KM, Pineda R 2nd, Tweeten JP, *et al*. Cataract in the adult eye preferred practice pattern®. Ophthalmology 2017;124:P1-119.
30. 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;120:687-94.
31. Reinstein DZ, Archer TJ, Gobbe M, Silverman RH, Coleman DJ. Epithelial thickness in the normal cornea: Three-dimensional display with artemis very high-frequency digital ultrasound. J Refract Surg 2008;24:571-81.
32. Reinstein DZ, Archer TJ, Gobbe M, Silverman RH, Coleman DJ. Stromal thickness in the normal cornea: Three-dimensional display with artemis very high-frequency digital ultrasound. J Refract Surg 2009;25:776-86.
33. Reinstein DZ, Archer TJ, Gobbe M. Refractive and topographic errors in topography-guided ablation produced by epithelial compensation predicted by 3D Artemis VHF digital ultrasound stromal and epithelial thickness mapping. J Refract Surg 2012;28:657-63.
34. R Rocha KM, Perez-Straziota CE, Stulting RD, Randleman JB. Epithelial and stromal remodeling after corneal collagen cross-linking evaluated by spectral-domain OCT. J Refract Surg 2014;30:122-7.
35. Reinstein DZ, Archer TJ, Gobbe M. Corneal epithelial thickness profile in the diagnosis of keratoconus. J Refract Surg 2009;25:604-10.
36. Edorh NA, El Maftouhi A, Djerada Z, Arndt C, Denoyer A. New model to better diagnose dry eye disease integrating OCT corneal epithelial mapping. Br J Ophthalmol 2022;106:1488-95.
37. Buffault J, Zéboulon P, Liang H, Chiche A, Luzu J, Robin M, *et al*. Assessment of corneal epithelial thickness mapping in epithelial basement membrane dystrophy. PLoS One 2020;15:e0239124.
38. Simon G, Ren Q, Kervick GN, Parel JM. Optics of the corneal epithelium. Refract Corneal Surg 1993;9:42-50.
39. Kolb-Wetterau C, Shajari M. IOL calculation in patients with Fuchs' endothelial dystrophy. In: Shajari M, Priglinger S, Kohnen T, Kreutzer TC, Mayer WJ, editors. Cataract and Lens Surgery. Cham: Springer; 2023. p. 223-5.



Supplementary Figure 1: Repeated measures correlation calculated of selected variables with 5mm (panels a, c, e, g, i) and 7mm central stromal thickness (CST) maps (panels b, d, f, h, j). Uncorrected distance visual acuity (UDVA - panels a and b), best corrected twilight vision (TV - panels c and d), and contrast sensitivity function (CSF) at spatial frequencies 1,5 cpd (CS B -panels e and f), 3 cpd (CS C - panels g and h) and 18 cpd (CS F - panels i and j). Light green dots represent individual 8am measurements, light blue dots represent 2pm and dark blue represent 8pm measurement timepoints. Colored lines show regression fits for each timepoint. Repeated measures were calculated with rmcorr R package