Detecting Subclinical Corneal Edema Using Corneal Thickness Mapping in Patients Presenting Fuchs Endothelial Corneal Dystrophy

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• **PURPOSE:** **To determine whether local corneal thickness changes observed with optical coherence tomography (OCT) can detect subclinical corneal edema in Fuchs endothelial corneal dystrophy (FECD).**

• **SETTING:** **Retrospective cohort study.**

• **METHODS:** **A series of patients presenting FECD who underwent cataract surgery alone (45 eyes) or with concomitant Descemet membrane endothelial keratoplasty (triple procedure; 117 eyes). The study reviewed medical records, collected the preoperative corneal thickness map and calculated the differences and ratio of corneal thickness measured at 5, 7, and 9 mm from the central corneal thickness. Area under the receiver operating characteristic curves (AUCs) were calculated and thresholds were selected to obtain a specificity of 90%.**

• **RESULTS:** **The median difference between 5- and 2-mm corneal thickness in the supra-nasal quadrant (Δ5-2mmSN) was 38 µm (interquartile range 34-46) in the cataract group and 17 µm (2-38) in the triple procedure group ($P < .001$). The corneal thickness ratios of supra-nasal 5- to 2-mm (R5/2mmSN) and 7- to 2-mm (R7/2mmSN) were 1.07 (1.06-1.08) and 1.15 (1.13-1.17)] in the cataract group and 1.03 (1.00-1.06) and 1.09 (1.06-1.14) in the triple procedure group ($P < .001$). The probability of corneal edema was increased 7-fold with Δ5-2mm SN < 27 µm (AUC = 0.76) and 9.4- and 7.4-fold with R5/2mmSN and R7/2mmSN < 1.045 (AUC = 0.77) and 1.118 (AUC = 0.76), respectively.**

• **CONCLUSIONS:** **Local changes in corneal thickness may be useful in detecting preclinical corneal edema, especially in patients with FECD undergoing cataract surgery.**

(Am J Ophthalmol 2023;246: 58–65. © 2022 Published by Elsevier Inc.)

AJO.com Supplementary Material available at AJO.com

Accepted for publication September 14, 2022.

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INTRODUCTION

PHACOEMULSIFICATION WITH INTRAOCULAR LENS implantation surgery in patients presenting Fuchs endothelial corneal dystrophy (FECD) remains a challenge. Determining whether the surgery should be performed alone or concomitantly with endothelial transplantation (triple procedure) is essential when the risk of postoperative endothelial decompensation is considered too high. Several clinical methods have aimed to identify patients at high risk of postoperative endothelial decompensation, including: symptoms experienced by the patients themselves (eg, morning blurred vision), FECD grade on slit-lamp examination, and corneal assessment with central corneal thickness (CCT) or endothelial cell density (ECD). However, the performance of the above indices in predicting postoperative endothelial dysfunction remains limited[1] because of inter-individual variability of CCT (with difficulty choosing a fixed threshold) and heterogeneity of preclinical corneal edema distribution in the cornea.[2] Several authors have tried to define objective preoperative criteria to search for subclinical edema,[1-5] the measurement of which is independent of corneal thickness or ECD per se. Using corneal topography mapping, the authors[4,5] suggested that some predefined local variations in corneal thickness could help diagnose preclinical edema, which is strongly considered a risk factor for postoperative endothelial decompensation and therefore suggests the immediate performance of a triple procedure. Additionally, Patel and associates[6] demonstrated that pseudophakic eyes with FECD and a tomography pattern suggestive of subclinical edema had altered best-corrected photopic and mesopic visual acuity and straylight compared with eyes with normal corneas.

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2022.09.014

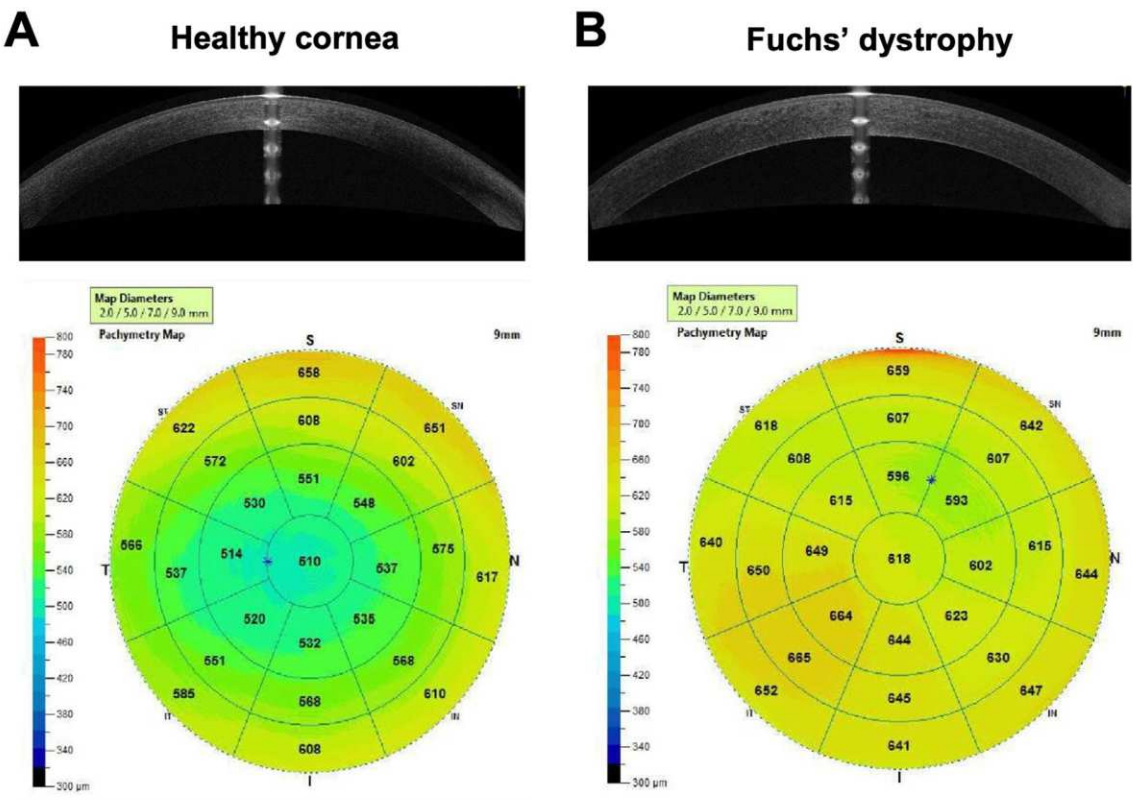

FIGURE 1. Corneal thickness mapping using optical coherence tomography (OCT) in a healthy cornea (A) and a cornea with Fuchs dystrophy (B).

By using non-contact, non-invasive, cross-sectional visualization of the cornea, optical coherence tomography (OCT) enables accurate measurement of the corneal thickness, with accurate thickness mapping at different preset locations of the cornea (mapping; Figure 1). A study comparing OCT features between patients with FECD and healthy individuals showed differences in corneal thickness mapping that were limited to CCT and also at 3 and 6 mm from the corneal center.[7] Hence, the search for preclinical edema may not be limited to measuring CCT alone, but a range of local values and changes might be considered during evaluation.[7] Moreover, CCT features a wide range of inter- and intra-individual variability. In fact, peripheral corneal thickness is heterogenous in all quadrants, known to be generally thicker in the nasal than temporal quadrants.[8] Concerning the above corneal features, studying changes in pachymetry using OCT corneal thickness mapping data could allow for the development of indices of local corneal thickness variation, which may predict preclinical corneal edema.

Providing objective and reproducible corneal measurements may help practitioners detect subclinical edema for accurately deciding between cataract surgery alone or a triple procedure.

This study examined changes in corneal thickness by using OCT mapping in patients presenting FECD who underwent cataract surgery or a triple procedure. It was hypothesized that specific tomographic patterns could predict subclinical edema in FECD. The analysis of the patterns together with their respective cutoff points may help surgeons manage these challenging cases.

MATERIALS AND METHODS

• **STUDY DESIGN AND PARTICIPANTS:** This was a monocentric retrospective study conducted at Rothschild Foundation Hospital, Paris, France, between January 2018 and May 2021. Approval was obtained from the Ethics Committee and the Rothschild Foundation Institutional Review Board IRB 00012801 (study no. CE_20201124_4_DGT). The study adhered to the tenets of the Declaration of Helsinki and the International Council for Harmonization Good Clinical Practice guidelines. It included: (1) patients without FECD (hereafter called "Cataract w/o guttae"); (2) patients with FECD (hereafter called "Cataract w/ guttae"; grade 3 or higher on the Krachmer classification) who underwent cataract surgery; (3) patients with FECD who underwent a triple procedure (hereafter called "Triple procedure") including cataract surgery with intraocular lens implantation and concomitant Descemet membrane endothelial keratoplasty (DMEK); and (4) pseudophakic patients with endothelial decompensation who underwent DMEK alone (hereafter designated "DMEK"). Patients without FECD who underwent cataract surgery had no guttae. Patients with FECD (grade 3 or higher on the Krachmer classification) who underwent cataract only had no morning vision blurring or clinical edema. Patients with FECD who underwent a triple procedure had morning vision blurring or suspicious edema defined as subtle thickening of the slit-lamp beam centrally relative to the peripheral cornea or clinical definite edema obvious on slit-lamp examination based on thickening of the stroma, Descemet or deep stromal folds, stromal clouding determined by sclerotic scatter, microcystic epithelial edema or bedewing, or subepithelial bullae, as defined by Sun and associates.[4] Patients who underwent DMEK alone had definite edema, as described above, secondary to cataract surgery.

• **DATA COLLECTION AND ANALYSIS:** The medical charts of eligible patients were reviewed. Demographic information was collected for each patient, including age at presentation, sex, and ophthalmological history. Data concerning clinical examinations at baseline were also collected. These data included measurement of initial and final best corrected visual acuity (BCVA), which was converted by using the logarithm of the minimum angle of resolution (logMAR) scale for statistical analysis, slit-lamp examination, and Goldmann applanation tonometry. Spectral-domain OCT imaging involved using an Optovue XR-Avanti (Optovue, Inc.) to measure preoperative CCT. Because the choice of corneal thickness thresholds does not account for inter-individual variations in the corneal thickness or study intra-individual changes, this study aimed to assess corneal thickness changes progressively from the center to the periphery in the different quadrants for all patients. Therefore, after measuring corneal thickness at 5, 7, and 9 mm from the center (2 mm), the differences in thickness measured at 5, 7, and 9 mm from the CCT (Δ5-2mm, Δ7-2mm, and Δ9-2mm, respectively) were calculated and adjacent measurement differences (ie, the change in corneal thickness from 5 to 7 mm [Δ7-5mm] and from 7 to 9 mm [Δ9-7mm]) were reported. Then the respective adjacent ratios of corneal thicknesses (eg, R5/2mm, R7/2mm, R9/2mm, R7/5mm, and R9/7mm) were measured. All these measurements (thickness differences and ratios) were realized in each of the 8 quadrants (infra-nasal [IN], nasal [N], infra-temporal [IT], temporal [T], supra-temporal [ST], superior [S], and supra-nasal [SN]). The absence of postoperative endothelial decompensation in patients with FECD was defined as recovery after cataract surgery with a final BCVA $\leq$ 0.1 logMAR (ie, $\geq$ 20/25) for at least 9 months postoperatively.

• **STATISTICAL ANALYSIS:** Categorical variables are presented as number (percentage). Continuous variables are presented as median (interquartile range). For continuous variables, statistical analysis involved the Kruskal–Wallis test and a post hoc analysis, limited to comparing patients with Fuchs dystrophy who underwent cataract and a triple procedure with Dunn's multiple comparison test. Significance was considered at $P < .05$ or adjusted for multicomparison. A multivariate analysis with logistic regression was then performed. Receiver operating characteristic (ROC) curves, which show the true positive rate (sensitivity) as a function of the false positive rate (1-specificity) for different cut-off values of a diagnostic test, were generated to discriminate patients with Fuchs dystrophy who underwent cataract surgery or a triple procedure. The performance of the discriminators was assessed by calculating the area under the ROC curve (AUC). Analyses involved using R (Development Core Team, 2020) and graphs were created with Prism (GraphPad Software).

RESULTS

• **BASELINE CHARACTERISTICS:** This study included 301 eyes in 226 patients (136 females [60%]); 32 (14%) patients formed the "Cataract w/o guttae" group, 32 (14%) the "Cataract w/ guttae" group, 91 (41%) the "Triple procedure" group, and 71 (31%) the "DMEK" group. Characteristics of eyes are summarized in Table 1. For all groups combined, the median (± interquartile range) age was 72 ± 5 years.

Preoperative BCVA was 0.3 ± 0.3 LogMAR in the "Cataract w/o guttae" group, 0.3 ± 0.2 LogMAR in the "Cataract w/ guttae" group, 0.4 ± 0.3 LogMAR in the "Triple procedure" group, and 0.6 ± 0.3 LogMAR in the "DMEK" group (Table 1). All measured corneal thickness values are presented in Supplementary Table S1 to Supplementary Table S3. The CCT was comparable between the "Cataract w/o guttae" and "Cataract w/ guttae" groups (522 ± 37 and 535 ± 38 µm, respectively) but was slightly increased in the "Triple procedure" and "DMEK" groups (586 ± 70 and 626 ± 80 µm, respectively) Supplementary Figure S2.

For a given measurement, for all quadrants and at all measurement positions (ie, central, 2, 5, 7, or 9 mm), the median corneal thickness was consistently highest in the "DMEK" group, followed by the "Triple procedure", "Cataract w/ guttae", and "Cataract w/o Guttae" groups. For example, the median corneal thickness at 5 mm in the supra-nasal quadrant was 631 µm (601-677) in the "DMEK" group, 605 µm (573-642) in the "Triple procedure" group, 579 µm (561-605) in the "Cataract w/ guttae" group, and 565 µm (541-581) in the "Cataract w/o Guttae" group ($P < .001$). Globally, the groups significantly differed in these corneal thickness values, which suggests that the corneal thickness differed between the groups. Because of the large amount of data and that this was not the main goal of the study, a post hoc pairwise comparison was not performed between groups.

TABLE 1. Characteristics of Eyes (301 Eyes; 226 Patients).				
	Cataract w/o Guttae (n = 59)	Cataract w/ Guttae (n = 45)	Triple Procedure (n = 117)	DMEK (n = 80)
CCT (μm)	522 ± 37	535 ± 38	586 ± 70	626 ± 80
BCVA (LogMAR)	0.3 ± 0.3	0.3 ± 0.2	0.4 ± 0.3	0.6 ± 0.3

Data are median (interquartile range). BCVA = best corrected visual acuity; CCT = central corneal thickness; DMEK = Descemet membrane endothelial keratoplasty; LogMAR = logarithm of the minimum angle of resolution; Triple procedure = cataract surgery, intraocular lens implantation and concomitant DMEK; w/ = with; w/o = without.

• **CORNEAL THICKNESS DIFFERENCE:** Corneal thickness changes were assessed from the center to the periphery in the different quadrants by calculating differences in thickness measured at 5, 7, and 9 mm from the center (Δ5-2mm, Δ7-2mm, and Δ9-2mm, respectively) or reporting adjacent measurements variations (Δ7-5mm and Δ9-7mm). Data are summarized in Supplementary Table S4 to Supplementary Table S8 and Supplementary Figure S2. As expected, the difference in corneal thickness increased the farther away from the center in all healthy and diseased corneas. However, the difference in corneal thickness between 5 and 2 mm (Δ5-2mm; Supplementary Table S4) did not significantly differ between the groups for all quadrants, especially in the inferior and temporal quadrants. Additionally, the difference in corneal thickness between 9 and 7 mm (Δ9-7mm; Supplementary Table S8) did not significantly differ among the groups for all quadrants, especially in the nasal, superior, supra-nasal, and supra-temporal quadrants; therefore, the variation in corneal thickness in these areas might be less suitable for detecting corneal edema.

Corneal thickness differences were close between the "Cataract w/o guttae" and "Cataract w/ guttae" groups. However, corneal thickness differences were lower in the "Triple procedure" than "Cataract w/ guttae" group. This observation was even more pronounced when analyzing the data from the "DMEK" group, which showed lower values than those for the "Triple procedure" group. For example, the median corneal thickness difference between 5 and 2 mm in the supra-nasal quadrant was 38 μm (32-46) in the "Cataract w/o Guttae", 38 μm (34-46) in the "Cataract w/ guttae" group, 17μm (2-38) in the "Triple procedure" group, and 11 μm (–9 to 36) in the "DMEK" group ($P < .001$). Therefore, edema may induce central corneal thickening with reduced corneal thickening that is normally observed from the center to the periphery. This observation is evidenced by summing the differences in corneal thickness across all quadrants, which were significantly lower in the groups that did not undergo endothelial keratoplasty (Supplementary Table S9).

The study then focused on comparing these differences between the groups that underwent cataract surgery alone ("Cataract w/ guttae" group) or a triple procedure ("Triple procedure" group), the main objective being to define indices allowing for detecting subclinical corneal edema (Supplementary Figure S2). On post hoc analysis comparing the corneal thickness difference between the "Cataract w/ guttae" and "Triple procedure" groups, the corneal thickness between 5 and 2 mm (Δ5-2mm) was significantly higher in all quadrants in the "Cataract w/ guttae" than the "Triple procedure" group, except in the inferior and temporal quadrants. For example, the median corneal thickness difference between 5 and 2 mm in the supra-nasal quadrant (Δ5-2mm SN) was 38 μm (34-46) in the "Cataract w/ guttae" group and was lower in the "Triple procedure" group (17 μm [2-38], $P < .001$). Likewise, the corneal thickness difference between 7 and 2 mm (Δ7-2mm) was significantly higher in all quadrants in the "Cataract w/ guttae" than the "Triple procedure" group, except in the temporal and infra-temporal quadrants. For example, the median corneal thickness difference between 7 and 2 mm in the supra-nasal quadrant (Δ7-2mm SN) was 80 μm (73-92) in the "Cataract w/ guttae" group and was lower in the "Triple procedure" group (53 μm [33-85], $P < .001$). Likewise, the corneal thickness difference between 9 and 2 mm (Δ9-2mm) and 7 and 5 mm (Δ7-5mm) was significantly higher in all quadrants in the "Cataract w/ guttae" than the "Triple procedure" group and that between 9 and 7 mm (Δ9-7mm) was significantly higher in all quadrants, except in the supra-temporal, superior, supra-nasal, and nasal quadrants.

The performance of these indices was then studied by ROC curves, estimating the AUC, and defining thresholds to obtain a specificity > 90%. The AUC values for central pachymetry, differences in corneal thickness by quadrant (ie, Δ5-2mm, Δ7-2mm, Δ9-2mm, Δ7-5mm, and Δ9-7mm) and the sums of the differences are summarized in Supplementary Table S10 to Supplementary Table S12. After logistic regression using the differences associated with the highest AUC values for each index, only corneal thickness difference between 5 and 2 mm in the supra-nasal quadrant (Δ5-2mm SN) remained a significant predictor (AUC = 0.76; Table 2 and Figure 2). Considering a specificity of 90%, a threshold of 27 μm was defined for corneal thickness differences between 5 and 2 mm in the supra-nasal quadrant (Δ5-2mm SN) to distinguish patients with Fuchs dystrophy who underwent cataract surgery or triple procedure. This threshold suggests that a patient with a Δ5-2mm SN < 27 μm has preclinical or clinical edema. Thus,

TABLE 2. Summary of Area Under Receiver Operating Characteristic Curve (AUC) of Corneal Thickness Difference in Patients With Fuchs Dystrophy Who Underwent Cataract Surgery Alone or a Triple Procedure.

Indices	Cataract	Triple Procedure	AUC (± SE)	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	LR+
Δ5-2mm SN	38 μm [34-46]	17 μm [2-38]	0.76 ± 0.04	< 27 μm	62% (53-71)	91% (79-98)	7.0
R5/2mm SN	1.07 [1.06-1.08]	1.03 [1.00-1.06]	0.77 ± 0.04	< 1.045	62% (53-71)	93% (82-99)	9.4
R7/2mm SN	1.15 [1.13-1.17]	1.09 [1.06-1.14]	0.76 ± 0.04	< 1.118	66% (56-74)	91% (79-99)	7.4
R9/2mm N	1.19 [1.16-1.22]	1.12 [1.09-1.19]	0.74 ± 0.04	< 1.137	54% (50-68)	91% (79-98)	6.1

Data are median (interquartile range). CI = confidence interval; LR+ = positive likelihood ratio; N = nasal; SE = standard error; SN = supra-nasal.

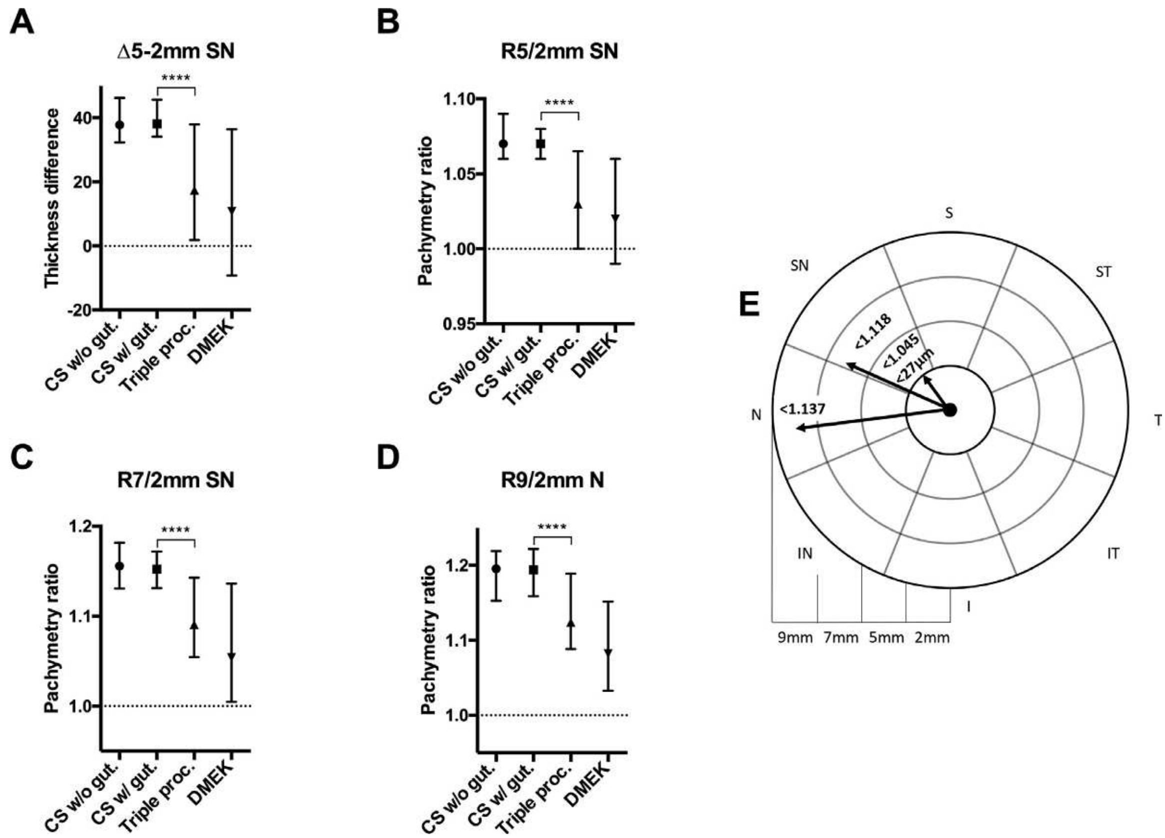

FIGURE 2. Plots of the median and interquartile range of the Δ5-2mm supra-nasal corneal thickness difference (A) and ratios of 5/2mm supra-nasal (B), 7/2mm supra-nasal and 9/2mm nasal (E) corneal thickness in the different groups of patients. Schematic representation of the statistically significant indices to detect corneal edema (E).

the probability of corneal edema is increased by 7-fold with a corneal thickness difference between 5 and 2 mm < 27 μm at the supra-nasal quadrant (Δ5-2mm SN < 27μm). Using the sum of the differences as an index did not provide better diagnostic performance (Supplementary Table S12).

• **CORNEAL THICKNESS RATIO:** Ratios of corneal thicknesses were also calculated rather than the differences detailed previously, which may have limited inter-individual variability. The corneal thickness ratios by quadrant (ie, R5/2mm, R7/2mm, R9/2mm, R7/5mm, and R9/7mm) are summarized in Supplementary Table S13 to Supplementary Table S17 and Supplementary Figure S3. As with the calculation of differences, all ratios significantly differed overall between groups, except for R5/2mm at the inferior and temporal quadrants and R9/7mm at the superior, supra-nasal, and supra-temporal quadrants. Post hoc analysis confirmed that ratios were significantly higher in the “Cataract w/ guttae” than the “Triple procedure” group (except for R5/2mm inferior and temporal, R7/2mm temporal and infra-temporal, and R9/7mm supra-temporal, superior supra-nasal, and nasal). For example, the median R5/2mm in the supra-nasal quadrant was 1.07 (1.06-1.08) in the

"Cataract w/ guttae" group and lower in the "Triple procedure" group (1.03 [1.00-1.06], $P < .001$). Likewise, the median R7/2mm in the supra-nasal quadrant was 1.15 (1.13-1.17) in the "Cataract w/ guttae" group and lower in the "Triple procedure" group (1.09 [1.06-1.14], $P < .001$). The median R9/2mm in the nasal quadrant was 1.19 (1.16-1.22) in the "Cataract w/ Guttae" group and lower in the "Triple procedure" group (1.12 [1.09-1.19], $P < .001$).

The performance of these indices was then studied by ROC curves, estimating the AUC, and defining thresholds to obtain a specificity of > 90%. The AUC values for corneal thickness ratio by quadrant (ie, R5/2mm, R7/2mm, R9/2mm, R7/5mm, and R9/7mm) are summarized in Supplementary Table S18. After logistic regression, including the index with the highest AUC values per index, the ratio of 5- to 2-mm corneal thickness in the supra-nasal quadrant (R5/2mm SN), 7- to 2-mm corneal thickness in the supra-nasal quadrant (R7/2mm SN), and 9- to 2-mm corneal thickness in the nasal quadrant (R9/2mm N) remained significant predictors; the AUCs were 0.76, 0.76, and 0.74, respectively. Considering a specificity of 90%, thresholds of 1.045, 1.118, and 1.137 for R5/2mm SN, R7/2mm SN, and R9/2mm N were defined, respectively, to distinguish patients with Fuchs dystrophy who underwent cataract surgery or a triple procedure and to detect preclinical edema. Therefore, the probability of corneal edema was increased 9.4-fold with an SN corneal thickness ratio of 5 to 2 mm < 1.045 (R5/2mm SN < 1.045). The ratios associated with the highest AUC values are summarized in Figure 2 and Table 2.

DISCUSSION

Identifying patients with Fuchs dystrophy and preclinical corneal edema at risk of endothelial decompensation after cataract surgery is essential to suggest a triple procedure. This identification requires the development of objective and reproducible criteria to identify these challenging cases. The evolution of grafting techniques, particularly the development of endothelial grafting techniques such as DMEK, has enabled a relatively standardized triple procedure to be performed with rapid postoperative visual recovery. The obvious presence of preoperative corneal edema, observed during slit-lamp examination, or the presence of morning vision blurring indicate endothelial dysfunction; however, these features may be absent, especially in cases of preclinical corneal edema.[1] Moreover, with the absence of a clear established threshold, ECD is an insufficient criterion to predict the risk of postoperative endothelial decompensation.[1] The clinical classification of Fuchs dystrophy is based on evaluation of the distribution of guttae;[9] however, when using this classification, Repp and associates[2] observed poor interobserver agreement. Furthermore, the FECD stage established by this classification is not always related to the presence of corneal edema.[2]

The CCT measurement is an objective tool that can identify corneal edema, thus reflecting endothelial dysfunction. Central corneal thickness was one of the first objective measurements used to assess the risk of postoperative endothelial decompensation. In 2004, Seitzman and associates[3] attempted to define a CCT threshold at which a triple procedure should be considered. At that time, endothelial decompensation was managed by performing penetrating keratoplasty. However, with the increasing adoption of DMEK in the management of FECD, the surgeon's choice of graft indication, particularly penetrating keratoplasty versus DMEK, may differ given the potential differences in terms of speed of visual recovery and postoperative complications. Seitzman and associates[3] determined that a threshold of 640 µm should prompt consideration of a triple procedure. Additionally, the disadvantage of a CCT threshold is that it does not account for inter-individual differences in CCT; thus, the same level of CCT may reflect edema in one individual but not in another. This situation is reflected in previous papers that demonstrated a moderate correlation between CCT and the risk of postoperative endothelial decompensation.[1-3] To refine the detection of subclinical edema without being limited to the measurement of CCT alone, Repp and associates[2] took into account concomitant central and pericentral pachymetry to create a ratio (central-to-peripheral thickness ratio) evaluated at 3, 3.6, and 4 mm. The results showed a modification of these ratios measured on corneas of patients with FECD compared with normal corneas; however, the correlation of these ratios with the stage of Fuchs dystrophy was moderate.

Sun and associates[4] described topographic changes in FECD patients with subclinical and clinical edema, namely: the loss of parallel isopachs, displacement of the thinnest point of the cornea, and focal posterior corneal surface depression. These parameters are independent of the CCT. Interestingly, Patel and associates[5] demonstrated that the loss of regular isopachs, displacement of the thinnest point, and the presence of posterior surface depression were risk factors for FECD progression. Additionally, they demonstrated that the 4-year cumulative risk of disease progression and 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.[5]

Nowinska and associates[7] compared corneal parameters measured with Swept-Source OCT in patients with FECD and healthy patients. In addition to an increase in CCT, the authors found an increase in the central 3- and 6-mm asymmetry indices and the posterior Ectasia Screening Index. These results underline the interest of not limiting the search for subclinical and clinical edema to the study of CCT alone but to also take into consideration the pericentral pachymetry and its variations.

To provide other objective and reproducible corneal measurements that may help practitioners detect subclinical corneal edema and accurately decide between cataract surgery alone or a triple procedure in FECD patients, this study examined and compared adjacent corneal thickness differences and ratios with OCT at different preset points of the cornea in different quadrants. As previously discussed, it was hypothesized that specific cut-off points could predict subclinical edema in FECD and may be a guideline for surgeons in these challenging cases. Corneal thickness is known to increase progressively from the center toward the periphery in healthy corneas; however, this increase is not homogeneous and largely depends on the quadrant considered. In fact, as highlighted, this increase is less marked in the temporal than nasal quadrant in healthy corneas. However, patients with clinical edema ("DMEK" group in this study) show reduced increase in corneal thickness from the center to the periphery, reflected by a reduction in the differences and ratios of corneal thickness from the periphery to the center. The variability in these measurements between patients manifests the inter-individual heterogeneity. In addition, the magnitude of the change in corneal thickness is heterogenous, including in patients with corneal edema, which also reflects the heterogeneity of the edema distribution. Sometimes a focal predominance of the edema can be observed. Thus, determining a single index to detect the presence of subclinical or clinical corneal edema is difficult.

For the study of criteria to discriminate patients with Fuchs dystrophy who underwent cataract alone or a triple procedure, because of subclinical or clinical corneal edema, some modifications of the ratios or differences in corneal thickness between the center and periphery were observed. Determining the periphery/center ratio enabled local variation in the pachymetry to be considered and the inter-individual variations in corneal thickness to be eliminated, as would be the case for considering CCT alone. Specifically, by using ROC curves to study the performance of previously described indices and then defining thresholds to obtain a specificity of $> 90\%$, it was found that the probability of corneal edema was increased 7-fold with a corneal thickness difference between 5 and 2 mm < 27 µm at the supra-nasal quadrant (Δ5-2mm SN < 27 µm) and 9.4-fold with an SN corneal thickness ratio of 5 to 2 mm $<$ 1.045 (R5/2mm SN $<$ 1.045). These predefined indices may represent parameters that could help surgeons detect subclinical edema and therefore help decide between cataract surgery alone or a triple procedure in FECD patients. Nevertheless, a prospective clinical trial is needed to validate these indices.

This study had limitations: (1) it was a retrospective monocentric study with a relatively small sample size and that included both eyes for some patients; (2) the heterogeneity of the corneal thickness measurements and indices studying the center/periphery pachymetry variation in the triple procedure group could partly be explained by the selection of patients with varying degrees of clinical edema in this group. This heterogeneity in the edema explained the rather low sensitivity that was observed. A subdivision of these patients in a prospective study could help refine the results. (3) Because of the study design, a preoperative and postoperative comparison of adjacent corneal thickness differences and ratios in all quadrants would have been of great value to determine more precise and reproducible parameters to specifically identify FECD patients at risk of postoperative corneal decompensation.

To conclude, the decision to perform cataract surgery alone or a triple procedure in patients presenting FECD still requires a tailor-made approach. This study found differences in local pachymetry changes (eg, Δ5-2mm SN, R5/2mm SN, R7/2mm SN, and R9/2mm N) between patients with Fuchs dystrophy who underwent cataract or a triple procedure that could help detect subclinical edema. Further prospective studies with larger sample sizes are warranted to validate these results.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and none were reported.
Funding/Support: None.
Financial Disclosures: None. All authors attest that they meet the current ICMJE criteria for authorship.

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