Corneal Densitometry as a Predictive Diagnostic Tool for Visual Acuity Results After Descemet Membrane Endothelial Keratoplasty

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• PURPOSE: We sought to investigate correlations between preoperative corneal backscatter with visual acuity results after Descemet membrane endothelial keratoplasty (DMEK) in eyes with corneal endothelial disorders.

• DESIGN: Retrospective interventional case series.

• METHODS: The first 551 consecutive patients with DMEK at the Center of Ophthalmology, University of Cologne who had available preoperative corneal densitometry values (corneal light backscatter measured in gray scale units) measured with the Scheimpflug-based Oculus Pentacam corneal densitometry module were screened for eligibility. Best spectacle-corrected visual acuity (BSCVA) results were retrospectively correlated with densitometry data. Densitometry data were obtained in 4 corneal layers (ie, anterior, central, posterior, and total layers) and 4 annuli. Pre- and postoperative BSCVA results were correlated with densitometry data. Receiver operating characteristic analyses were performed.

• RESULTS: Four hundred twelve eyes were available for the analyses. Visual acuity results improved significantly after DMEK surgery at 3, 6, 12, and 24 months of follow-up ($P < .001$). Corneal backscatter correlated moderately with preoperative BSCVA results. Moderate associations to postoperative BSCVA results could predominantly be found between densitometry values of the anterior and central layer more pronounced in the center of the cornea for all postoperative timepoints. The posterior layer correlated worst with postoperative gain in BSCVA. Receiver operating characteristic analyses revealed that the best predictive power of densitometry values was for the 2-6 mm annular zone of the cornea.

• CONCLUSION: Corneal backscatter in eyes with corneal endothelial disorders correlates with postsurgical BSCVA results after DMEK surgery. Therefore, early DMEK surgery seems to have a positive impact on long-term BSCVA results. (Am J Ophthalmol 2019;198:124–129. © 2018 Elsevier Inc. All rights reserved.)

DESCEMET MEMBRANE ENDOTHELIAL KERATOplasty (DMEK) is a suitable treatment option for most patients who have endothelial dysfunction. DMEK offers the advantages of low rejection rates and rapid visual recovery. The increasing popularity of DMEK surgery leads to increasing demands on visual acuity results, which depend on the final corneal transparency.

Several corneal changes may affect vision in eyes with endothelial pathologies, such as corneal edema, corneal scarring, and surface irregularities.[1–3] So far, visual acuity and corneal pachymetry have been used to quantify disease progression and morphological as well as functional improvement after DMEK.[4] Corneal imaging has evolved in the past few decades, and the Scheimpflug principle is a new objective method for monitoring corneal transparency. The Oculus Pentacam (Pentacam HR; Oculus GmbH, Wetzlar, Germany) uses the Scheimpflug principle and takes 50 cross-sectional images of the entire anterior segment within 2 seconds in a noncontact method, providing complete corneal pachymetry, corneal topography, and densitometry, a measure of scattering of the light.[5,6] Densitometry is routinely used for long-term monitoring of corneal transparency after corneal collagen cross-linking or refractive surgery.[4]

In a previous study we found that corneal densitometry improved after DMEK surgery in eyes with Fuchs endothelial dystrophy (FED) during the follow-up period (2 years). Moderate correlations with visual acuity results could be detected.[7]

We investigated whether preoperative corneal backscattering can predict postsurgical visual acuity results.

METHODS

DATA OF THE FIRST 1000 CONSECUTIVE EYES WITH ENDOthelial disorders that underwent DMEK surgery at the Department of Ophthalmology, University of Cologne, Germany, between July 2011 and September 2016 were

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reviewed retrospectively. The main inclusion criterion was availability of preoperative densitometry values measured by a Scheimpflug-based Oculus Pentacam corneal densitometry module (Pentacam HR; Oculus GmbH, Wetzlar, Germany).

Five hundred fifty-one cases presented with available preoperative densitometry data, and 449 cases were excluded.

DMEK surgery was performed in eyes with corneal endothelial disorders, and in most cases this was FED (Table 1). The surgeons decided to perform DMEK surgery if conservative treatment was no longer effective because of significant corneal edema causing blurred vision.

• **CORNEAL DENSITOMETRY:** Corneal densitometry (corneal light backscatter) is expressed in gray scale units (GSUs) and ranges from 0 (100% transparent) to 100 (completely opaque or 0% transparent).[8] Corneal backscattered light values were analyzed using the Cornea Densitometry Average Table (version 1.20r29), and values were obtained in 4 annular zones of the cornea. The zones are centered on the apex of the cornea, the first zone being 2 mm in diameter (central annular zone 0-2 mm), the second zone 2-6 mm in diameter, the third zone 6-10 mm in diameter, and the fourth zone 10-12 mm in diameter.[9,10] The analyses are provided for 4 corneal layers, including an anterior layer (AL; first 120 μm), a posterior layer (PL; posterior 60 μm), a central layer (CL; volume between anterior and posterior layer without a fixed thickness), and a total layer (TL; volume between the epithelium and endothelium of the cornea).[9,10]

For each measurement, corneal light backscatter values of the central annular zone of diameter from 0-2 mm and of a peripheral zone from 2-10 mm of the cornea's AL, CL, PL, and TL were analyzed.

The most peripheral annular zone (10-12 mm) has not been included into our analysis because its reproducibility and repeatability were so weak in a previous normative study.[10]

• **CLINICAL OUTCOME PARAMETER:** Collected clinical data included best spectacle-corrected visual acuity (BSCVA), central corneal thickness (CCT) (Pentacam HR; Oculus GmbH, Wetzlar, Germany), and donor graft characteristics. Donor ECD was measured using the phase-contrast microscope (Axiovert 25; Zeiss, Oberkochen, Germany).

Clinical outcome parameters were assessed at baseline (preoperatively) and at 3, 6, 12, and 24 months postsurgery.

Exclusion criteria included complex pathologies of the anterior or posterior segment or previous corneal surgeries. If both eyes of 1 patient underwent DMEK, only 1 eye was randomly selected.

Sixty-eight fellow eyes and 65 eyes with history of corneal transplantation (penetrating keratoplasty in 23 cases, DMEK in 30 cases, and Descemet stripping automated endothelial keratoplasty in 12 cases) and 6 eyes with complex pathologies of the anterior segment were excluded. Four hundred twelve eyes were available for the analyses. For statistical analysis, BSCVA results were converted to logarithm of the minimum angle of resolution (logMAR) and eyes with extracorneal visual limitations were excluded (n = 73).

Clinical data have been compiled within the Cologne DMEK database, using REDCap electronic data capture tools.[7,11] The study was approved by the local institutional review board (14-373) and was conducted

TABLE 1. Clinical Baseline Data of the Study Cohort (n = 412)

Age	69.9 ± 10.6 years
Gender	
Female, n (%)	265 (64)
Male, n (%)	147 (36)
Indication	
FED, n (%)	369 (9%)
PBK, n (%)	37 (%)
PEX keratopathy, n (%)	6 (1)
Surgery	
Phakic DMEK, n (%)	25 (6)
Pseudophakic DMEK, n (%)	204 (50)
Triple DMEK, n (%)	183 (44)
Baseline BSCVA (logMAR), mean ± SD	0.50 ± 0.36
Donor age (y), mean ± SD	67.3 ± 11.2
Donor ECD cells/mm^{2}mean ± SD	2712.7 ± 241.6
Baseline densitometry values (GSU), mean ± SD	
Anterior layer	
0-2 mm	49.9 ± 20.0
2-6 mm	42.7 ± 16.2
6-10 mm	47.0 ± 19.4
Total	46.1 ± 14.0
Corneal layer	
0-2 mm	27.1 ± 10.3
2-6 mm	24.5 ± 8.7
6-10 mm	33.3 ± 11.5
Total	29.4 ± 8.2
Posterior layer	
0-2 mm	24.9 ± 6.7
2-6 mm	21.8 ± 5.6
6-10 mm	27.5 ± 7.2
Total layer	25.7 ± 5.4
0-2 mm	34.0 ± 10.8
2-6 mm	29.6 ± 9.5
6-10 mm	35.7 ± 10.4
Total	33.8 ± 8.5

BSCVA = best spectacle-corrected visual acuity; DMEK = Descemet membrane endothelial keratoplasty; ECD = endothelial cell density; FED = Fuchs endothelial dystrophy; GSU = gray scale unit; logMAR = logarithm of the minimum angle of resolution; PBK = pseudophakic bullous keratopathy; PEX = pseudoexfoliation; SD = standard deviation.

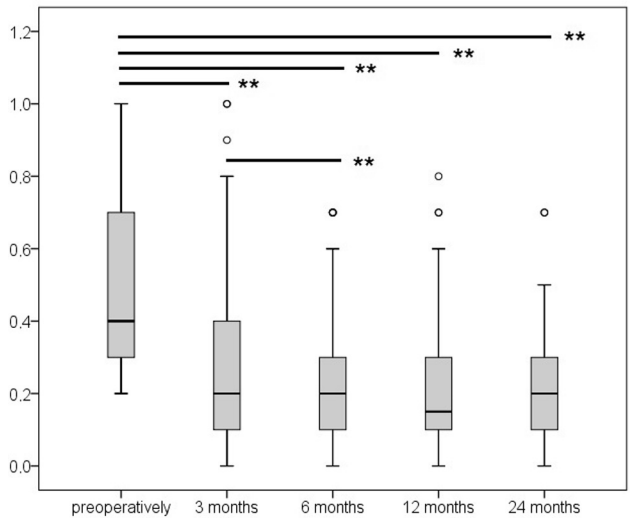

FIGURE 1. Best spectacle-corrected visual acuity (BSCVA) results before and after Descemet membrane endothelial keratoplasty. Box plots for BSCVA (in logarithm of the minimum angle of resolution) results are shown before Descemet membrane endothelial keratoplasty (preoperatively), and at 3, 6, 12, and 24 months of follow-up. Boxes represent first quartile, median, and third quartile values; whiskers represent extreme values. **Statistically significant changes in BSCVA values ($P < .001$).

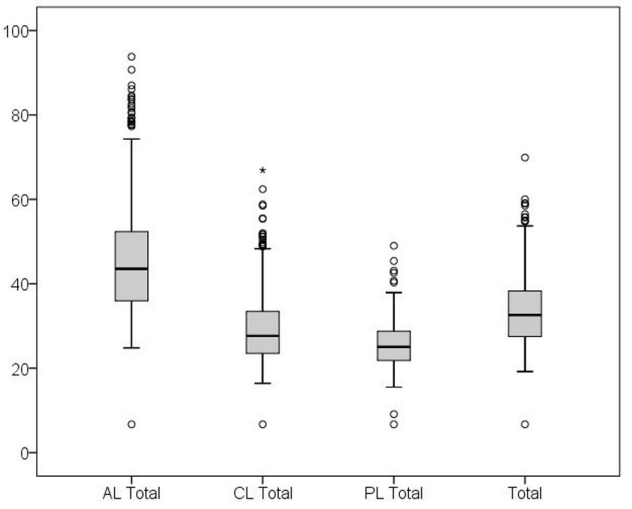

FIGURE 2. Corneal light backscatter before Descemet membrane endothelial keratoplasty. Box plots for average corneal densitometry values in gray scale units are shown before Descemet membrane endothelial keratoplasty for the anterior (AL), central (CL), posterior (PL) and total corneal layers. Boxes represent first quartile, median, and third quartile values; whiskers represent extreme values.

in adherence to the tenets of the Declaration of Helsinki.

• **SURGICAL TECHNIQUE:** DMEK surgery was performed in a standardized fashion by 2 experienced surgeons as either a single procedure or as a triple procedure (combined with cataractextraction and posterior chamber lens implantation) for eyes with coexistent cataract formation.[7,12] In short, the DMEK graft was prepared by stripping of the Descemet membrane from the donor corneoscleral rim before transplantation using forceps.[13,14] Following descemetorhexis, a cataract-shooter was used to insert the graft into the anterior chamber. Unfolding of the graft lamella was then performed using a no-touch technique. When needed, an air bubble was used to move the graft into the correct position. After centering and unfolding the graft, the anterior chamber was filled completely with air or sulfur hexafluoride 20% to secure the graft at the recipient's posterior corneal surface.

Before surgery, a neodymium-doped yttrium aluminium garnet iridotomy at 6 o'clock was performed to avoid postoperative angle block with intraocular pressure decompensation.

After DMEK, all patients were hospitalized for approximately 1 week and received standardized topical treatment in form of topical prednisolone acetate 1% in tapering doses over 12 months (once daily after 4 months) and topical antibiotic eye drops for 1 to 2 weeks as well as lubricant eyes drops (5 times/day) as long as needed.[15] Pilocarpine 1% eye drops were applied 3 times a day as long as the anterior chamber was filled with air covering the pupil's bottom margin. Patients were instructed to remain supine for at least 3 days postoperatively.[16]

• **STATISTICAL ANALYSES:** Data were analyzed with SPSS software (version 22.0 for Windows; SPSS, Inc, Chicago, IL, USA) and with the programming language RV (version 3.2.2; R Foundation for Statistical Computing, Vienna, Austria). BSCVA results were converted to logMAR.

Analyses included descriptive analysis, Student *t* test for significance testing for interval scale parameters (BSCVA), and correlation using the Pearson correlation coefficient. According to the value r, the correlation was interpreted as perfect (exactly ± 1), strong (±0.70), moderate (±0.50), or weak (±0.30) depending on which value r was closest to. Diagnostic power was assessed by the receiver operating characteristic analysis to calculate the area under the curve. The greater the area under the curve, the more accurate the test. The level of significance was defined as $P < .05$.

RESULTS

CLINICAL OUTCOME PARAMETER AND DESCPRITIVE ANALysis of the overall study cohort is shown in Table 1.

• **BSCVA:** BSCVA results increased significantly after DMEK surgery from a mean 0.50 ± 0.36 logMAR to 0.21 ± 0.17 logMAR after 3 months ($P < .001$) and steadily

TABLE 2. Correlations Between Preoperative Corneal Densitometry Values and Visual Acuity Results

	0-2 mm	2-6 mm	6-10 mm	Total
Pearson correlation between preoperative corneal densitometry values and preoperative BSCVA results				
AL	0.526 ($P < .001$)	0.624 ($P < .001$)	0.455 ($P < .001$)	0.584 ($P < .001$)
CL	0.550 ($P < .001$)	0.578 ($P < .001$)	0.336 ($P < .001$)	0.528 ($P < .001$)
PL	0.178 ($P < .001$)	0.313 ($P < .001$)	0.150 ($P = .002$)	0.215 ($P < .001$)
TL	0.539 ($P < .001$)	0.611 ($P < .001$)	0.374 ($P < .001$)	0.541 ($P < .001$)
Pearson correlation between preoperative corneal densitometry values and gain in BSCVA results 6 months postsurgery				
AL	−0.369 ($P < .001$)	−0.405 ($P < .001$)	−0.183 ($P = .002$)	−0.341 ($P < .001$)
CL	−0.401 ($P < .001$)	−0.409 ($P < .001$)	−0.111 ($P = .066$)	−0.299 ($P < .001$)
PL	−0.130 ($P = .031$)	−0.228 ($P < .001$)	−0.022 ($P = .718$)	−0.109 ($P = .07$)
TL	−0.386 ($P < .001$)	−0.409 ($P < .001$)	−0.136 ($P = .024$)	−0.312 ($P < .001$)
Pearson correlation between preoperative corneal densitometry values and gain in BSCVA results 12 months postsurgery				
AL	−0.367 ($P < .001$)	−0.392 ($P < .001$)	−0.152 ($P = .012$)	−0.332 ($P < .001$)
CL	−0.412 ($P < .001$)	−0.392 ($P < .001$)	−0.112 ($P = .065$)	−0.302 ($P < .001$)
PL	−0.241 ($P < .001$)	−0.313 ($P < .001$)	−0.055 ($P = .369$)	−0.177 ($P = .003$)
TL	−0.409 ($P < .001$)	−0.411 ($P < .001$)	−0.147 ($P = .015$)	−0.325 ($P < .001$)
Pearson correlation between preopertaive corneal densitometry values and gain in BSCVA results 24 months postsurgery				
AL	−0.467 ($P < .001$)	−0.466 ($P < .001$)	−0.236 ($P = .008$)	−0.406 ($P < .001$)
CL	−0.455 ($P < .001$)	−0.414 ($P < .001$)	−0.180 ($P = .045$)	−0.345 ($P < .001$)
PL	−0.171 ($P = .058$)	−0.216 ($P = .016$)	−0.062 ($P = .492$)	−0.132 ($P = .143$)
TL	−0.461 ($P < .001$)	−0.436 ($P < .001$)	−0.200 ($P = .026$)	−0.359 ($P < .001$)

AL = anterior layer; BSCVA = best spectacle-corrected visual acuity; CL = central layer; TL = total layer.

increased to 0.12 ± 0.10 logMAR after 2 years ($P < .001$). Gains in visual acuity were statistically significant for all postsurgical time points ($P < .001$) compared with visual acuity at registration. In addition, BSCVA significantly increased between the 3- and 6-month follow-ups. During the course, a further increase in BSCVA was measured without statistical significance (Figure 1).

• **CORNEAL DENSITOMETRY:** Detailed results of corneal densitometry values can be found in Table 1. Average values for all layers are presented in Figure 2.

• **CORRELATIONS BETWEEN CORNEAL DENSITOMETRY VALUES AND BSCVA RESULTS:** Preoperative corneal densitometry values correlated moderately for all zones and all layers with preoperative BSCVA results (Table 2). Moderate associations to postoperative BSCVA results could predominantly be found between corneal densitometry values of the AL and CL and were more pronounced in the second annular zone (2-6 mm) of the cornea for all postoperative time time points (Table 2). The posterior layer showed only weak correlations in the second annular zone with postoperative gain in BSCVA.

Receiver operating characteristic analyses revealed poor predictive power of densitometry values using 12-month postoperative BSCVA results (0.2 logMAR cut-off point). Detailed results can be found in Table 3. The best predictive power was found for the second zone (2-6 mm).

DISCUSSION

FED, THE MAIN INDICATION FOR DMEK, LEADS TO A LOSS OF corneal endothelial cells and the accumulation of anomalous collagenous deposits on the Descemet membrane as it progresses centrifugally, leading to central corneal edema and visual impairment. Peripheral corneal endothelial cells and Descemet membrane remain relatively unaffected until advanced stages of the disease.[17,18]

Different parameters, including CCT and visual acuity, can be used to monitor disease progression, and changes

TABLE 3. Diagnostic Power of Preoperative Corneal Densitometry Values Assessed by Receiver Operating Characteristic Analyses

	0-2 mm	2-6 mm	6-10 mm	Total
AL	0.606	0.669	0.683	0.696
CL	0.595	0.677	0.644	0.667
PL	0.492	0.578	0.582	0.585
TL	0.597	0.667	0.654	0.67

AL = anterior layer; AUC = area under the curve; CL = central layer; PL = posterior layer; ROC = receiver operating characteristic; TL = total layer.

Receiver operating characteristic analyses–areas under the curve. The cutpoint was best spectacle-corrected visual acuity 0.2 logarithm of the minimum angle of resolution 12 months postoperatively.

are important for clinical decision making and the timing of corneal transplantation. Different subjective and objective grading classifications exist,[19] but until recently there has been no definite recommendation regarding when surgery should be performed or how the "perfect" time point for DMEK can be defined. Surgeons have increasingly performed surgery earlier during the disease course because of the increasing standardization of the procedure and the decreasing rate of complications. However, whether an earlier transplantation acutally results in better visual acuity or if there is a preferred time point at which DMEK should be performed has not been defined.

Corneal densitometry is a feasible method providing objective surveillance of corneal transparancy.[4,7] In patients with corneal endothelial disorders, disruption of the collagen matrix because of corneal edema (and later during the disease course, corneal scarring) provokes an increase in light scattering that is clinically identified as corneal haze.[20] Therefore, changes in corneal densitometry values in the anterior layer of the cornea and preferrably in the second annular zone (2-6 mm) can be measured.[4,7] One reason why increased backscatter in the second zone is best for the identification of patients with lower visual acuity after DMEK could be that the involvement of midperipheral corneal regions indicates progressed stages of the disease. Densitometry values of the posterior layer correlated worst with visual acuity results, although it presents the diseased layer of the cornea in endothelial disorders. The reason may be that the clinically relevant stromal edema is placed in another layer—the CL. In addition, corneal edema may lead to subepithelial changes that lead to a reduction in visual acuity in affected patients. Therefore, correlations between visual acuity and corneal densitometry seem to be more expected in the CL or AL than in the PL.

In a previous study, we showed that corneal densitometry values improve postoperatively after DMEK without a correlation to the extent of corneal edema (as measured by CCT). Postoperatively, correlations could be found between densitometry and BSCVA, but not between densitometry values and CCT or ECD or between CCT and BSCVA.[7]

Although some data exist regarding corneal densitometry in FED or in eyes after DMEK, no clear evidence for a potential predictive value of densitometry is available. One of the limitations of our study is its retrospective design. It would be desirable to collect data of eyes with corneal endothelial diseases prospectively to form a more even distribution of different stages of the disease. However, our cohort comprises patients with corneas at an early as well as progressed stages of the disease, with visual acuities ranging from very low to almost normal BSCVA. In addition, supplementary evaluation and correlation of findings of slit-lamp examination in conjunction with corneal densitometry measurements would be interesting. Data regarding this aspect are still missing and should best be addressed by further prospective analysis.

Another limitation of our study is that 449 eyes of the first 1000 consecutive DMEKs had to be primarily excluded because preoperative corneal desitometry data were missing. Initially, the measurement of corneal densitometry before DMEK had not been implemented as a routine examination in our department. Therefore, the presence of a selection bias cannot be excluded. In the meantime, we have introduced the examination using the Pentacam as a standard examination before DMEK, and we are looking forward to performing further evaluations in larger cohorts in the future.

Nevertheless, we found an association between preoperative backscattering and postoperative visual acuity results in eyes with endothelial dystrophies after DMEK. Our results support corneal surgeons in the decision-making process to perform DMEK before the formation of corneal scars caused by chronic edema.

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