Predicting Corneal Improvement after Descemet Membrane Endothelial Keratoplasty for Fuchs Endothelial Corneal Dystrophy

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Purpose: To develop a model to predict corneal improvement after Descemet membrane endothelial keratoplasty (DMEK) for Fuchs endothelial corneal dystrophy (FECD) from Scheimpflug tomography.

Design: Cross-sectional study.

Participants: Forty-eight eyes (derivation group) and 45 eyes (validation group) with a range of severity of FECD undergoing DMEK.

Methods: Scheimpflug images were obtained before and after DMEK. Before DMEK, pachymetry map and posterior elevation map patterns were quantified by a special image analysis program measuring tomographic features of edema (loss of regular isopachs, displacement of the thinnest point of the cornea, posterior surface depression). Image-derived novel parameters were combined with instrument-derived parameters, and the relative influences of parameters associated with the change in central corneal thickness (CCT) after DMEK in the derivation group were determined by using a gradient boosting machine learning model. The parameters with highest relative influence were then fit in a linear regression model. The derived model was applied to the validation group. Correlations and agreement were assessed between predicted and observed changes in CCT.

Main Outcome Measures: Predictive power (R^2) and mean difference between predicted and observed change in CCT.

Results: The gradient boosting machine model identified 4 novel parameters of isopach circularity and eccentricity and 1 instrument-derived parameter (posterior surface radius); preoperative CCT was a poor predictor. In the derivation group, the model strongly predicted the change in CCT after DMEK ($R^2 = 0.80$; 95% confidence interval [CI], 0.71–0.89) and the mean difference between predicted and observed change was, by definition, 0 μm. When the same 5 parameters were fit to the validation group, the model performed very highly ($R^2 = 0.89$; 95% CI, 0.84–0.94). When the coefficient estimates from the derivation model were used to predict the change in CCT in the validation group, the predictive power was also high ($R^2 = 0.78$; 95% CI, 0.68–0.88), and the mean difference was 4 μm (predicted minus observed).

Conclusions: Scheimpflug tomography maps of corneas with FECD can predict the improvement in CCT after DMEK, independent of preoperative corneal thickness measurement. The model could be applied in clinical practice or for clinical research of FECD. *Ophthalmology Science 2022;2:100128 © 2022 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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Fuchs endothelial corneal dystrophy (FECD) encompasses a wide range of severity based on the functional state of the corneal endothelium. When corneal edema is detectable biomicroscopically, patients usually have vision symptoms, and in advanced cases may also have pain resulting from bullae. Treatment of FECD is indicated when edema is detectable biomicroscopically, and Descemet membrane endothelial keratoplasty (DMEK) usually results in a reduction of central corneal thickness (CCT) with improvement in vision.[1] When

biomicroscopically detectable corneal edema is not visible, patients still can be symptomatic because of the presence of subclinical edema.[2] Subclinical edema can be detected by assessing for 3 specific patterns in Scheimpflug tomography posterior elevation and pachymetry maps, and treatment by DMEK can also result in significant improvement of corneal function and vision and reduction in CCT.[2]

As the medical and surgical treatment landscape for FECD continues to evolve,[3] developing an objective method

of measuring edema and predicting improvement in corneal function will be important for clinical trial outcomes and for application in clinical practice.[4,5] We showed that Scheimpflug tomography can detect subclinical edema in FECD and can predict disease prognosis based on the presence of specific posterior elevation and pachymetry map patterns.[6] Importantly, this method is independent of CCT measurement, which was previously used as a guideline for when to consider keratoplasty in clinical practice; however, clinical decisions based on absolute values of CCT can result in inappropriate treatment (a change in CCT over time is more helpful than isolated values of CCT). Scheimpflug tomography has the potential to quantify corneal edema and its improvement with therapy objectively, and although such a model was recently proposed for this,[7] it was largely dependent on preoperative CCT, and therefore subject to the same caveats of using CCT measurements in clinical practice.[4,6] However, Scheimpflug pachymetry patterns are potentially more important than pachymetry values, and their quantification could provide an objective assessment of corneal edema and its improvement after therapy, with possible application in clinical trials of novel therapeutic agents.

In this study, we used novel quantitative parameters from Scheimpflug tomography posterior elevation and pachymetry maps to derive a model to predict the improvement in CCT after DMEK for FECD. Although using isolated values of CCT to determine whether to intervene in FECD is not recommended, resolution of corneal edema after an intervention can be easily summarized by the change in CCT before and after the intervention. Our model was developed in a derivation group and was independent of preoperative CCT. The model was tested in a separate validation group.

Methods

Participants

This study was approved by the Mayo Clinic Institutional Review Board and adhered to the tenets of the Declaration of Helsinki. The derivation group consisted of participants with FECD requiring DMEK who were recruited from the cornea service at Mayo Clinic, Rochester, MN, and enrolled in a prospective study of DMEK outcomes between September 2015 and October 2019; these subjects provided prospective informed consent. Eyes underwent Scheimpflug imaging before and at regular intervals after surgery. Fuchs endothelial corneal dystrophy was diagnosed by cornea specialists (S.V.P., K.H.B.) based on the presence of guttae; the distribution of guttae and the presence of clinically detectable edema were recorded. Eyes were excluded if previous or current corneal disease was present except FECD, or if there had been previous corneal or intraocular surgery except for uncomplicated phacoemulsification with endocapsular intraocular lens placement. Scheimpflug images were acquired before and at 6 months after DMEK, by which time all eyes had reached steady state (i.e., stable CCT, as determined by subsequent measurements).

The validation group was identified retrospectively and consisted of consecutive eyes with FECD requiring DMEK between October 2014 and December 2020 that met the same inclusion and exclusion criteria as the derivation group and also underwent Scheimpflug imaging before DMEK and 4 to 12 months after

DMEK. Authorization of data use for research was verified for these subjects. In addition, images acquired after DMEK had to date from after the cornea had reached steady state, as confirmed by stable CCT when images were obtained after DMEK.

Descemet Membrane Endothelial Keratoplasty Procedure

All eyes underwent DMEK by 2 cornea surgeons (S.V.P., K.H.B.) combined with phacoemulsification and endocapsular intraocular lens placement in phakic eyes. Surgery was performed through a clear corneal incision. All DMEK grafts had a diameter of 7.75 mm, were injected into the anterior chamber, were unscrolled with a no-touch technique, and were fixated to the posterior cornea with sulfur hexafluoride gas tamponade. Additional air or gas was placed after surgery if needed for graft detachment. Postoperative treatment included topical corticosteroid tapered to a maintenance low dose by 6 months.

Scheimpflug Image Analysis

All participants underwent Scheimpflug imaging (Pentacam HR; Oculus) before and after DMEK, as previously described.[8] Postoperative images, obtained at steady state, were used only to determine CCT (i.e., corneal thickness at the pupil center) by directly exporting the data using the instrument's software (Pentacam version 1.22r05). Preoperative images were used to determine CCT and for special analysis of the 4 Maps Refractive display derived by the instrument's software and meeting the instrument's software quality criteria. The 4 Maps Refractive displays were exported as high-resolution images devoid of any numeric or other markings over the posterior elevation and pachymetry color maps for subsequent analysis.

A special image analysis program was developed to automatically analyze the exported images (specifically, the posterior elevation and pachymetry maps) to provide quantitative parameters related to the key features of subclinical edema: irregular isopachs, displacement of the thinnest point of the cornea, and posterior depression. Ninety novel parameters were combined with 90 relevant instrument-derived parameters exported from the instrument's software for each image before DMEK as potential factors for predicting postoperative improvement in CCT after DMEK (Supplemental Table 1). Parameters derived from our special analysis quantified different aspects of the key features of subclinical edema and included measures of isopach regularity, displacement of the thinnest point from the pupil center, and volume of posterior tissue depression relative to a best-fit sphere. Instrument-derived parameters were also related to the posterior elevation and pachymetry maps and included radius and asphericity of the posterior surface and standard deviation of corneal thickness at different diameters from the center.

Statistical Analysis

Corneal improvement after DMEK was defined as the difference in CCT from before to after surgery. Central corneal thickness before and after DMEK was compared by using generalized estimating equation models to account for any correlation between fellow eyes of the same patient.

With a very large number of potentially important parameters for predicting the improvement in CCT, the initial analysis was completed by using a gradient boosting machine model[9] (a type of machine learning algorithm) for the derivation group data. The gradient boosting machine model determined the relative influence of each parameter for predicting improvement. The parameters with the highest relative influences were identified as
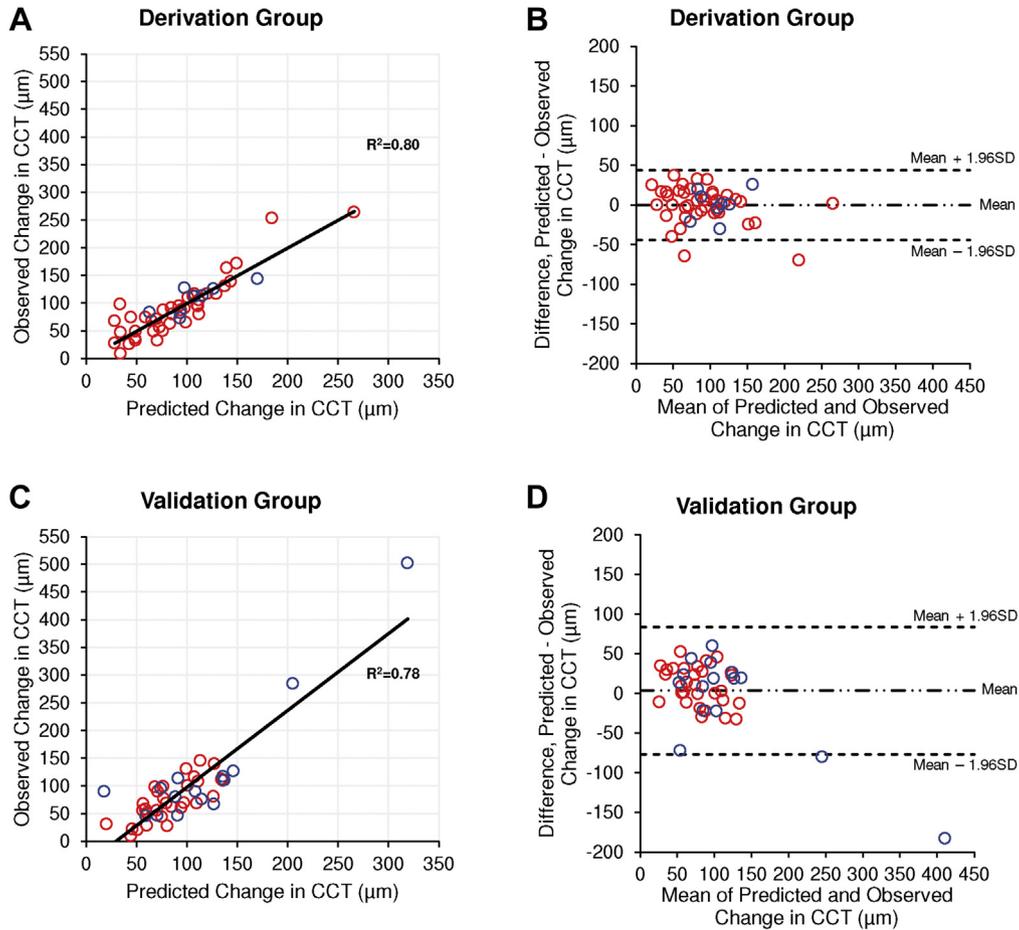
Figure 1. Graphs showing correlation and agreement between predicted and observed change in central corneal thickness (CCT) for derivation and validation groups. **A, B,** In the derivation group, (**A**) the model strongly predicted the change in CCT compared with the true change in CCT after Descemet membrane endothelial keratoplasty (DMEK; $R^2 = 0.80$), (**B**) and by definition, the mean difference was 0 μm. **C, D,** When the coefficient estimates obtained from the derivation group were applied to the validation group, (**C**) the model remained highly predictive of the change in CCT ($R^2 = 0.78$), and (**D**) the mean difference between predicted and observed change in CCT was 4 μm. The limits of agreement in the validation group (**D**), defined as the mean difference ± 1.96 standard deviations (SDs) of the difference, were wider than in the derivation group (**B**) because the model underpredicted the improvement in CCT in 1 eye. In all graphs, eyes that were phakic (typically with cataract) before DMEK are shown in red, and eyes that were pseudophakic (with a posterior chamber intraocular lens) are shown in blue; the trend lines shown are for all eyes combined.

key parameters, and these were then applied in standard logistic regression models to summarize the goodness-of-fit of the data. We restricted the number of key parameters to 5 for the logistic regression models, given the relatively small number of eyes. The impact of preoperative CCT was also assessed by deliberately including and excluding it in the final model.

The derived predictive model was then fit to the separate validation group data. First, the key parameters identified in the derivation group were assessed as predictors in the validation group by using coefficient estimates derived from the validation group. Second, the coefficient estimates from the derivation group were applied to the validation group to determine the predicted change in CCT, and goodness-of-fit was determined by comparing this with the observed (true) change in CCT.

The relationships between predicted and observed changes in CCT were assessed by using Pearson correlations, with goodness-of-fit assessed by R^2 values; the significance of correlations was assessed by using generalized estimating equation models. Mean differences between predicted and observed changes in CCT were assessed by using Bland-Altman plots,[10] and the limits of

agreement were the mean difference ± 1.96 standard deviations of the difference.

The cases of 2 patients from the validation group with images acquired in different years before DMEK are also described. Predicted changes in CCT for each image before DMEK were summarized to report how the model performed over time in these patients.

Results

Derivation Group

The derivation group consisted of 48 eyes of 39 patients; mean ± standard deviation age at surgery was 68 ± 7 years (range, 49–84 years), and 23 patients (59%) were women. Five eyes underwent 1 repeat air injection for partial graft detachment. The median time between acquiring preoperative tomography images and surgery was 8 days (range,
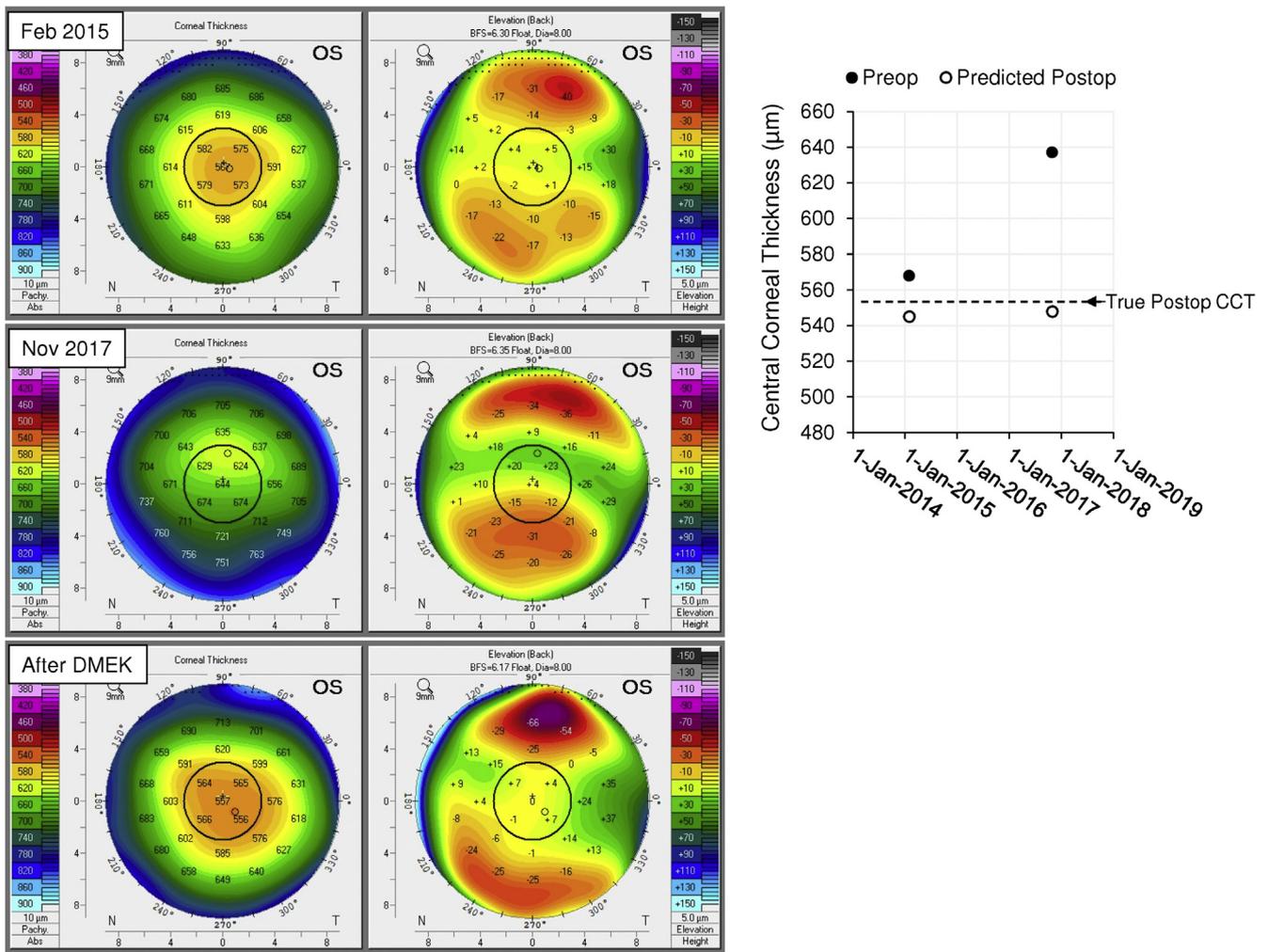
Figure 2. Predicting improvement in central corneal thickness (CCT) from Scheimpflug tomography in patient 1. In February 2015, Scheimpflug tomography maps of the left cornea of a 61-year-old woman with Fuchs endothelial corneal dystrophy showed subtle loss of round and oval isopachs in the pachymetry map, possible early posterior surface depression inferior to the central cornea, and CCT of 568 μm. From those maps, our model predicted a 23-μm improvement in CCT with Descemet membrane endothelial keratoplasty (DMEK), which would have resulted in a postoperative CCT of 545 μm; no intervention was taken at the time because the patient was asymptomatic. By November 2017, the condition had progressed with obvious loss of circular isopachs, displacement of the thinnest point of the cornea, and central posterior depression; CCT had increased to 637 μm, and our model then predicted 89 μm of improvement, which would have resulted in CCT of 548 μm after DMEK. Observed CCT at steady state after DMEK in February 2018 was 557 μm. OS = left eye; Preop = before surgery; Postop = after surgery.

1−72 days). Central corneal thickness improved by an average of 94 μm, from 630 ± 50 μm (range, 538−763 μm) before DMEK to 536 ± 40 μm (range, 456−618 μm) at 6 months after DMEK ($P < 0.001$). Central corneal thickness did not change between 6 and 12 months (538 ± 39 μm; range, 460−632 μm) after DMEK.

The relative influence of all possible parameters predictive of the improvement in CCT were summarized, and the 5 factors with the highest relative influence were included in the final model, which was:

$$\Delta CCT = 63.5 \times I_1 - 245.7 \times I_2 + 246.9 \times I_3 - 45.0 \times I_4 + 22.5 \times r_b + 44.9, \quad (1)$$

where ΔCCT was the change in central corneal thickness, I_1, I_2, I_3, and I_4 were parameters of isopach regularity, and r_b

was the radius of the flat meridian of the posterior corneal surface. Specifically, the parameters of isopach regularity were mean eccentricity of the central 10 isopachs (I_1), mean circularity of all isopachs (I_2), standard deviation of eccentricity of all isopachs (I_3), and standard deviation of circularity of all isopachs (I_4). Isopach circularity and eccentricity were calculated from standard formulae as 4π(area enclosed) / (perimeter)^2 and as the quotient of distance between foci and length of major axis of an ellipse, respectively.

Performance of this model was very high ($R^2 = 0.80$; 95% CI, 0.71−0.89; Fig 1A). The mean difference between predicted and observed change in CCT was, by definition, 0 μm (95% CI, −6 to 6 μm; Fig 1B). From the gradient boosting machine model, preoperative CCT was one of the weakest influencing parameters, and therefore was not
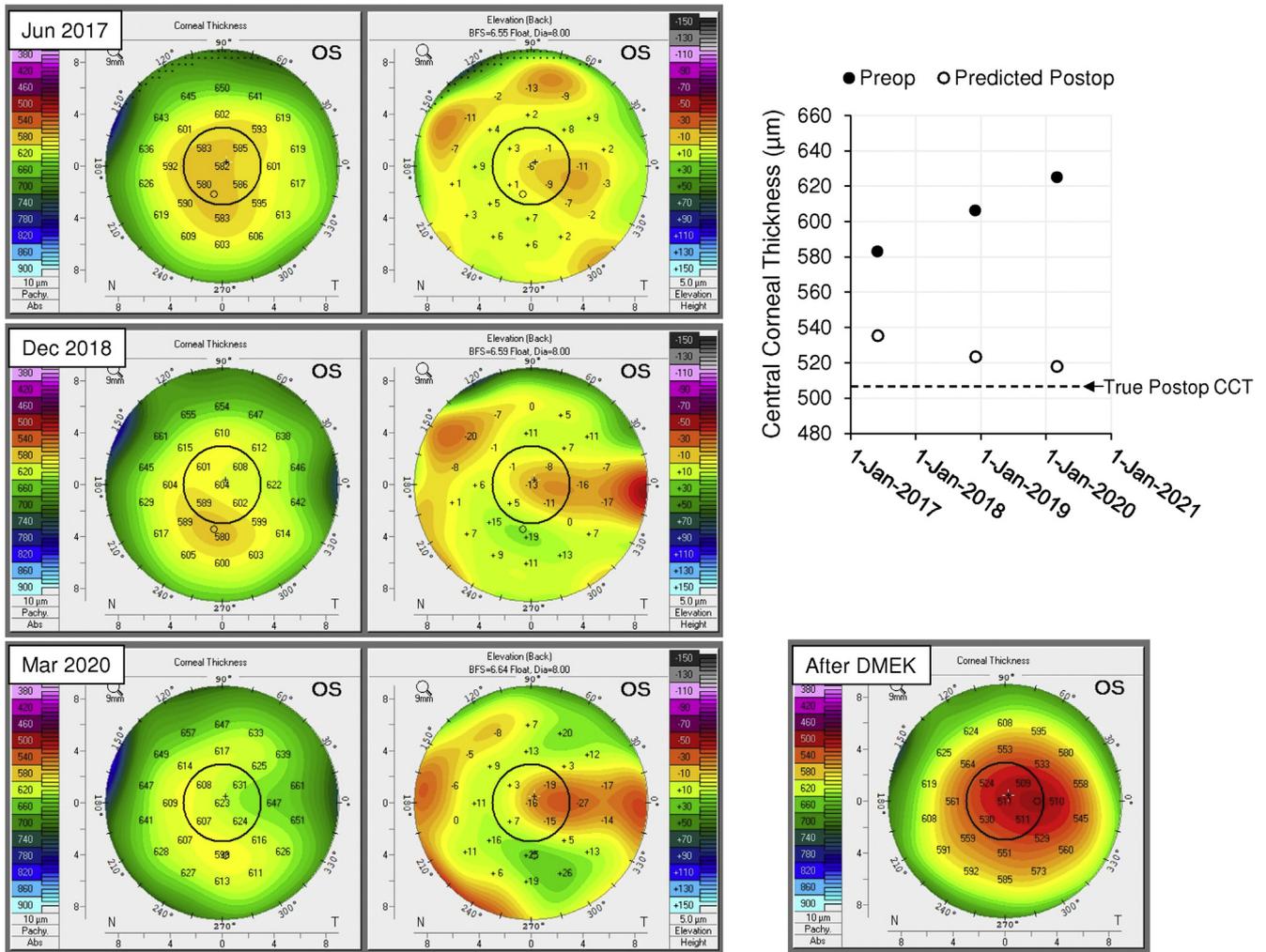
Figure 3. Predicting improvement in central corneal thickness (CCT) from Scheimpflug tomography in patient 2. In June 2017, Scheimpflug tomography maps of the left cornea of a 68-year-old woman showed irregular isopachs, displacement of the thinnest point, and focal posterior depression; although the patient had vision symptoms at that time, she deferred any intervention. Tomography images were repeated in December 2018 and March 2020 and showed worsening of the posterior elevation and pachymetry maps with a gradual increase in CCT. In June 2017, our model predicted 48 μm of improvement in CCT from 583 μm to 535 μm; in December 2018, the model predicted improvement of 83 μm, from 606 μm to 523 μm; in March 2020, the model predicted improvement of 107 μm, from 625 μm to 518 μm. Observed CCT at steady state after Descemet membrane endothelial keratoplasty (DMEK) in December 2020 was 509 μm. OS = left eye; Preop = before surgery; Postop = after surgery.

included in the final predictive model; as a result, when we deliberately included CCT in the final model, the performance of the model did not improve.

Validation Group

The validation group consisted of 45 eyes of 41 patients; age at surgery was 67 ± 8 years (range, 50−84 years), and 25 patients (61%) were women. Three eyes underwent 1 repeat air injection for partial graft detachment. The median time between acquiring preoperative tomography images and surgery was 49 days (range, 1−397 days). Central corneal thickness improved by an average of 91 μm, from 617 ± 72 μm (range, 513−982 μm) before DMEK to 526 ± 41 μm (range, 421−620 μm) at steady state after DMEK ($P < 0.001$).

When the same 5 parameters identified in the derivation model were fit to the validation data using coefficient estimates from the validation group only, the model performed very highly ($R^2 = 0.89$; 95% CI, 0.84−0.94). When the coefficient estimates from the derivation model were applied to the validation data (i.e., applying equation 1), the predicted change in CCT was strongly correlated with the observed change in CCT ($r = 0.88$; $P < 0.001$; n = 45), and therefore, the predictive power was high ($R^2 = 0.78$; 95% CI, 0.68−0.88; Fig 1C); the mean difference was 4 μm (predicted minus observed; 95% CI, −8 to 16 μm; Fig 1D).

Case Reports

Tomography images and clinical outcomes of 2 patients from the validation cohort are presented with respective predicted
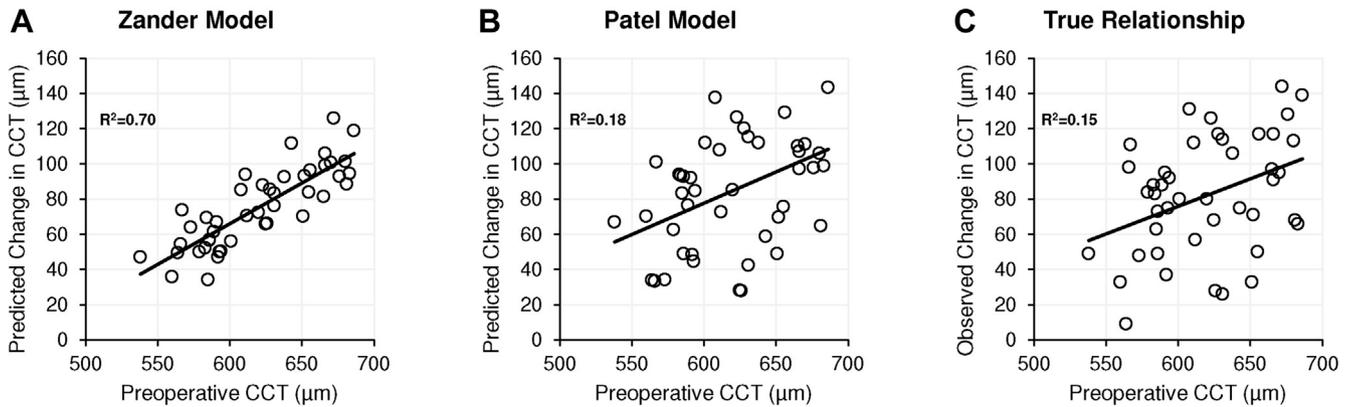
Figure 4. Scatterplots showing the role of preoperative central corneal thickness (CCT) in predicting the improvement in CCT after Descemet membrane endothelial keratoplasty. Zander et al[7] developed a model to predict the change in CCT that was strongly related to preoperative CCT. **A**, When our derivation data were analyzed with the Zander model, we found a strong relationship between preoperative CCT and the predicted change in CCT ($R^2 = 0.70$). **B**, However, with our model, preoperative CCT was poorly predictive of the change in CCT ($R^2 = 0.18$). **C**, In reality, preoperative CCT was poorly predictive of the true observed change in CCT ($R^2 = 0.15$), similar to that predicted by our model. Therefore, the Zander model mimics clinical decision-making based on cutoffs of preoperative CCT, which can be erroneous, whereas our model predicted changes in CCT from tomography map patterns independent of any corneal thickness measurement.

improvements in CCT (Figs 2 and 3). Both patients showed tomographic features consistent with subclinical edema in FECD at initial imaging, with subjective gradual worsening of the posterior elevation and pachymetry map patterns over time. In conjunction with progression of the map patterns, CCT also increased in both patients over time. In both patients, after applying the predictive model (equation 1) to each examination before DMEK, the predicted postoperative CCT was similar to that actually achieved at steady state after DMEK. In addition, as CCT increased over time before DMEK, the model predicted correspondingly greater improvements in CCT such that the predicted postoperative CCT for each eye remained relatively consistent for each examination.

Discussion

Potential improvement in CCT, an indicator of improved corneal endothelial function, after DMEK for FECD can be predicted from preoperative Scheimpflug tomography maps. This can help clinicians to counsel patients regarding the likelihood for improved corneal function, and presumably vision, after DMEK, and can provide confidence to surgeons that endothelial keratoplasty will benefit patients. The model we derived was highly predictive and could potentially be used in clinical research of FECD.

Improvement in CCT is expected in nearly all patients after DMEK, assuming sufficient edema is present, whether clinical or subclinical. We therefore used the change in CCT, derived in a consistent manner from Scheimpflug imaging before and after DMEK, as an objective measure of corneal endothelial function to develop the predictive model. All preoperative parameters considered for the model were derived from Scheimpflug tomography, and the model was independent of preoperative CCT or any other corneal thickness measurement. This is important because a wide range of normal CCT overlaps CCT in clinically

significant FECD,[11,12] and using CCT cutoffs can lead to erroneous patient management.[2,4] The 180 candidate parameters selected as potential predictors were based on their relevance to quantifying the tomographic patterns of edema, that is, irregular isopachs, displacement of the thinnest point of the cornea, and posterior surface depression.[2] The radius of the posterior corneal surface was the only instrument-derived parameter that was strong enough to be included in the final model and would have been affected by posterior surface depression.[13] The 4 strongest factors for the final model were parameters derived from our special analysis of isopach patterns in the pachymetry map (circularity and eccentricity); that is, they were all measures of isopach regularity. The final derived model was highly predictive of the change in CCT (from R^2, 80%), and the same parameters performed highly when fit to the validation group (from R^2, 88%). More importantly, applying the coefficient estimates of the derivation group to the validation group also resulted in high predictive power (from R^2, 78%). For the 2 patients with longitudinal data, the model predicted greater improvements in CCT over time as the degree of tomographic edema worsened (Figs 2 and 3), indicating the ability of the model to interpret different patterns and yet return a consistent result. Our model being independent of any corneal thickness measurement supports the importance of considering pachymetry map patterns more highly than absolute pachymetry values.[2,4,6]

Clinicians frequently encounter patients with FECD and cataract (or other comorbidities affecting vision) and need to determine whether corneal surgical intervention may be of benefit. Although we do not recommend basing surgical decisions solely on the predicted change in CCT, this predictive model could supplement clinical information to help make such decisions, especially when edema is not detectable biomicroscopically and historical CCT measurements are not available. It would have been ideal to predict the improvement in vision (instead of CCT) in this study, but

because most eyes were phakic with cataract before DMEK (Fig 1) and rendered pseudophakic after DMEK, assessment of vision would have been confounded by cataract. However, in otherwise healthy pseudophakic eyes with FECD, vision is unaffected when tomography patterns are normal, and vision is typically abnormal when tomography patterns are abnormal, indicating that vision is affected predominantly by edema, rather than by guttae.[14] Therefore, predicting the improvement in CCT (i.e., edema) after DMEK might be a surrogate for predicting improved vision in otherwise healthy eyes with FECD.

The derived model also may have a role for clinical trials of FECD by helping to define enhanced cohorts for enrollment and to stratify randomization for fair comparison. In addition, because successful DMEK almost certainly results in the maximum change in CCT of any current intervention for FECD, this predicted outcome measure could serve as a benchmark against which the effect of novel medical and surgical interventions, including Descemet stripping only,[15] can be compared. The model also might be better than using differences in CCT to assess disease progression in clinical research (Figs 2 and 3) because pachymetry map patterns are minimally affected by diurnal variations[16]; however, this determination requires significant further systematic investigation beyond the 2 patients shown with longitudinal data.

Recently, Zander et al[7] developed a model to predict corneal improvement in FECD after DMEK by using Scheimpflug imaging. They assessed predetermined parameters for predicting the change in CCT, including subjective categorical assessment of isopach irregularity and continuous assessment of posterior surface depression, corneal backscatter, and CCT. Of note, they assessed posterior surface depression as displacement from the best-fit sphere, rather than the volume of depressed tissue; we assessed several volumetric parameters in our study (Supplemental Table 1), but none were strong enough to be incorporated into the final model. We did not assess corneal backscatter because it is a poor predictor of prognosis[6] and requires significant additional image standardization.[17] The strongest factor in the model proposed by Zander et al was preoperative CCT; this is not surprising because change in CCT is calculated in part from preoperative CCT (i.e., these variables are related) and their model had few other candidate parameters. Indeed, when we applied the Zander et al[7] model coefficient estimates (using standardized backscatter) to our derivation data, we found that 70% (from R^2) of the predicted change in CCT was attributed to preoperative CCT (Fig 4), whereas in reality, only 15% (from R^2) of the observed change in CCT was explained by preoperative CCT (Fig 4). Predicting the presence of corneal edema in FECD from an isolated measurement of CCT is not possible, and therefore, models that are strongly dependent on preoperative CCT should be used with caution, if at all. As a result, the model by Zander et al[7] predicts more improvement in thicker preoperative corneas regardless of whether edema is present, and this is similar to erroneously making clinical practice decisions based on cutoffs of preoperative CCT. In contrast, our model assessed tomography map patterns independent of preoperative CCT (Fig 4) and showed much higher predictive power than the model by Zander et al.[7]

Our study is not without limitations. The limits of agreement for the validation group (Fig 1D) were wider than those of the derivation group (Fig 1B) because the model significantly underestimated the predicted change in CCT in 1 eye. Review of this eye showed profound diffuse corneal edema after cataract surgery (similar to that typically seen with pseudophakic corneal edema unrelated to FECD), but more typical FECD in the fellow eye, with 5 mm of central confluent guttae with tomographic edema. This indicates that our model may be less predictive for FECD with diffuse stromal edema (because circularity and eccentricity parameters will be influenced less by diffuse versus localized edema). However, our model performed well for the subclinical edema stage of the disease (because subclinical edema is more localized) and possibly even for subtle tomographic edema (see earliest data in Fig 2), which is important because these stages are more relevant to when clinical trial interventions are being considered and also when clinical decision-making is more challenging. Despite deriving a very strongly predictive model from a relatively small sample, however, opportunity to refine the model with a larger number of eyes remains. Another limitation is that the change in CCT after DMEK might not represent solely resolution of edema and will be affected partially by replacing thick abnormal Descemet membrane in FECD with thinner and healthier donor Descemet membrane.[18,19] Because we estimate the difference in Descemet membrane thickness between normal corneas and corneas with FECD to be 20 to 30 μm at most,[20] predicted improvements within this range from our model should be interpreted with caution. Finally, the special image analysis program needs user interface development before it can be made available to other investigators.

In summary, we developed a model to predict corneal improvement after DMEK for FECD by using Scheimpflug imaging parameters that were independent of corneal thickness. The model is derived from a special analysis of Scheimpflug images that yields novel parameters for measuring tomography map patterns. The method has potential application in clinical practice and clinical research.

Footnotes and Disclosures

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