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Graft Thickness at 6 Months Postoperatively Predicts Long-Term Visual Acuity Outcomes of Descemet Stripping Automated Endothelial Keratoplasty for Fuchs Dystrophy and Moderate Phakic Bullous Keratopathy: A Cohort Study

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Purpose: It remains unclear whether preoperative central graft thickness (CGT) contributes to visual outcomes of Descemet stripping automated endothelial keratoplasty (DSAEK). This retrospective cohort study examined the ability of preoperative and postoperative CGT to predict 12-month best spectacle–corrected visual acuity (BSCVA) after DSAEK for Fuchs endothelial corneal dystrophy/moderate pseudophakic bullous keratopathy/second graft.

Methods: All consecutive patients who underwent DSAEK in 2015 to 2018 were included. The primary end point was 12-month BSCVA. DSAEK-CGT was measured preoperatively and 6 times between postoperative day 8 and month 12. Eyes were divided according to preoperative CGT 130 μm (ultrathin-DSAEK threshold) or 6-month postoperative CGT 100 μm (mean 6-month postoperative DSAEK-CGT). The *t* test assessed CGT evolution of the 4 groups over time. Multivariate analyses examined whether preoperative CGT or 6-month CGT categories predicted 12-month BSCVA. Multivariate analysis assessed the preoperative/perioperative factors that predicted 6-month CGT.

Results: A total of 108 eyes (68 patients) underwent DSAEK. Preoperative CGT was >130 and ≤130 μm in 87 and 21 eyes, respectively. Postoperative CGT was >100 and ≤100 μm in 50 and 58 eyes, respectively. Thin 6-month postoperative grafts thinned significantly more relative to preoperative thickness than thick grafts ($P < 0.001$). Preoperative CGT subgroups did not show this difference. Six-month postoperative CGT ($P = 0.01$), but not preoperative CGT, predicted 12-month BSCVA. Preoperative CGT strongly predicted 6-month CGT ($P = 0.0003$).

Conclusions: Postoperative, but not preoperative, DSAEK-CGT predicted 6-month BSCVA. The correlation between preoperative and postoperative CGT and interstudy variation in preoperative CGT measurement accuracy may explain literature disparities regarding the importance of preoperative CGT in DSAEK outcomes.

Key Words: DSAEK, central graft thickness, visual acuity, Fuchs endothelial corneal dystrophy, pseudophakic bullous keratopathy

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In 2004, Melles described Descemet stripping automated endothelial keratoplasty (DSAEK)[1] for managing Fuchs endothelial corneal dystrophy (FECD) and moderate pseudophakic bullous keratopathy (PBK). In this posterior lamellar keratoplasty technique, a graft composed of posterior stroma, Descemet membrane, and endothelium replaces the diseased endothelium and its overlying Descemet membrane. This technique effectively restores the visual acuity in FECD and PBK cases[2–6] and has become a standard treatment for these pathologies.[7,8]

Two years after Melles proposed DSAEK, he developed Descemet membrane endothelial keratoplasty (DMEK), which is a technically demanding procedure that involves a graft composed only of Descemet membrane with endothelium.[3,4,9] Multiple studies then showed that DMEK seems to be superior to DSAEK in final postoperative best spectacle–corrected visual acuity (BSCVA).[10–15] In 2011, Neff et al speculated that the better performance of DMEK reflects its 10-fold thinner graft because they found that DSAEK grafts thinner than 131 μm yielded better final visual acuity than thicker grafts.[9,16] This led to the introduction in 2014 of ultrathin-DSAEK (UT-DSAEK) by Busin.[17] It uses a standard DSAEK graft that is thinned with a microkeratome, which removes much of the stroma and yields a preoperative graft thickness below 130 μm.[17–19]

A randomized clinical trial[20] and other studies[18,21] suggest that compared with conventional DSAEK, UT-DSAEK indeed seems to yield better final visual

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acuity. Several prospective and retrospective cohort studies even suggest that its visual outcomes approach those obtained after DMEK.[18,19,22–25] However, this was not observed in a recent randomized controlled trial[26] and several retrospective studies.[27–29] Other large studies have also failed to detect differences between UT-DSAEK and conventional DSAEK.[28,30] Moreover, Terry et al[31] reported that preoperative graft thickness accounted for only 5% of the visual improvement associated with DSAEK.

Our recent prospective cohort study may shed some light on a possible cause of these discrepancies. This study was conducted on 141 eyes with advanced PBK that underwent DSAEK; it showed that 6-month central graft thickness (CGT), but not preoperative CGT, was predictive of BSCVA at 6 months despite the fact that preoperative and postoperative CGT correlated closely.[32] These findings suggested that because there are many subtle factors that could shape preoperative CGT measurements (eg, type of storage, eye bank vs. surgeon cutting), it may be a highly variable (and therefore inadequate) measure of the intrinsic healthiness and potential performance of the graft, which is reflected more accurately by postoperative CGT.

However, our study had some limitations: It focused on patients with advanced PBK, who have intrastromal scars that can hamper visual recovery and thus may be more sensitive to intrinsic graft healthiness than other indications.[33] Moreover, final BSCVA was only measured at 6 months. Thus, to determine whether graft thickness either before or after DSAEK surgery influences final BSCVA in other indications and whether it exerts this effect over the long term, we identified patients with FECD, moderate PBK, or second graft who underwent DSAEK 1 year previously and analyzed their CGTs before and 6 months after surgery. The patients were then divided according to whether 1) their preoperative CGT was more or less than 130 μm or 2) their CGT at 6 postoperative months was more or less than 100 μm. The 130-μm threshold reflects a common definition of UT-DSAEK[16–19] while the 100-μm threshold reflects our previous finding that the average 6-month postoperative DSAEK graft thickness was 100 μm.[32]

PATIENTS AND METHODS

Study Design and Ethics

This retrospective single-center cohort study was performed in the Regional Metz-Thionville Hospital Center, Grand Est, France, and was approved by the Ethics Committee of the French Society of Ophthalmology (Institute Review Board 00008855 Société Française d'Ophtalmologie IRB #1). It was registered in ClinicalTrials.gov (Identifier: NCT04424550). All procedures were conducted in accordance with the principles of the Declaration of Helsinki. All patients were informed before surgery that their surgery-related data might be used for research. All consented to this possibility.

Patient Selection

The study cohort consisted of all consecutive patients with FECD or moderate PBK (defined as PBK without persistent intrastromal scarring and subepithelial bubbles and <800-μm corneal edema) or who required a second graft and who underwent DSAEK between September 2016 and September 2019 and were followed up for at least 12 months. 1) DSAEK was conducted rather than DMEK because the patients with FECD had a previous vitrectomy (which makes DMEK difficult to perform) or the surgery was conducted before our department decided to routinely use DMEK for all FECD cases; 2) DSAEK is preferred for PBK because the corneas are often quite altered at the time of the surgery, which complicates DMEK; and 3) in second graft cases, patients often prefer DSAEK to DMEK because it is simpler to perform. In all cases, surgery was conducted as soon as possible after diagnosis because the visual outcomes of DSAEK (and DMEK) correlate with the initial visual acuity.[34,35] Patients were excluded if they had ocular pathologies that could interfere with the final visual outcome (exudative or atrophic macular degeneration, glaucoma, advanced diabetic retinopathy, and maculopathy of any kind), primary graft failure, or a history of retinal detachment or vitreomacular surgery.

Preoperative Measurements

Before surgery, all patients underwent a complete ophthalmological examination. BSCVA was scored with reference to the logarithm of the minimum angle of resolution. Intraocular pressure was measured with Goldmann applanation tonometry. Objective refraction was measured using the autorefractometer VISIONIX L67 (LUNEAU SAS, Chartres, France) with the spherical equivalent. Endothelial cell density (ECD) was measured with nocontact specular microscopy (NIDEK CEM-530; NIDEK Co, Ltd). Biomicroscopic eye examination and anterior and posterior segment optical coherence tomography (OCT) (RS 3000; OCT RetinaScan Advance, NIDEK Co, Ltd.) were also conducted.

Surgery

All surgeries were performed by the same experienced surgeon (J.M.P.) using standardized surgical techniques. Although most patients underwent general anesthesia, the health status in some patients contraindicated this and peribulbar locoregional anesthesia with 7 mL of ropivacaine 7.5 mg/mL was used instead. If the patients were not already pseudophakic, they underwent simultaneous cataract surgery with phacoemulsification in a microcoaxial Microincision cataract surgery mode using the Stellaris PC platform (Bausch & Lomb, France).

Descemetorhexis was executed by marking the epithelium of the recipient with a 9-mm diameter marker (diameter marker for patient cornea #19095; Moria SA, Anthony, France) to guide the descemetorhexis and to allow the correct positioning and perfect centering of the transplanted donor flap. The 9-mm diameter endothelium and Descemet membrane of the patient were stripped and removed by using an inverted Price–Sinskey hook (Single-Use Price Hook #17302; Moria SA) under sterile air. A disposable inverted spatula was

TABLE 1. Demographic, Clinical, and Surgical Characteristics of the Eyes That Underwent DSAEK and Their Changes in BSCVA and CGT After Surgery

Characteristic	Mean ± SD or n (%)
Age, yr	76 ± 9
Female sex	71 (66)
Indication	
PBK	56 (52)
FECD	27 (25)
Second graft	25 (23)
Right eye operated	63 (58)
General anesthesia	81 (75)
Triple procedure	8 (7)
First graft	78 (72)
Graft age, yr	67 ± 12
Preop graft ECD, cells/mm^2	2505 ± 210
Operating time, min	33 ± 9
Complications	
Cystoid macular edema	1 (1)
Rejection episode	0 (0)
Rebubbling	7 (6)
Successful surgery*	108 (100)
CGT, μm	
Preoperative	164 ± 47
Day 8	136 ± 63
Day 15	120 ± 51
Month 1	110 ± 50
Month 3	105 ± 49
Month 6	103 ± 47
Month 12	104 ± 48
BSCVA, logMAR	
Preoperative	1 ± 0.37
Day 8	1.25 ± 0.33
Day 15	0.96 ± 0.34
Month 1	0.72 ± 0.3
Month 3	0.51 ± 0.23
Month 6	0.38 ± 0.16
Month 12	0.33 ± 0.17

*The success of the procedure was defined as a clear cornea with the graft in place and quantifiable visual acuity over 1 year follow-up.
Preop, preoperative; triple procedure, phaco-DSAEK.

also used as a supplement if necessary (single-use inverted 90 degrees spatula # 17305; Moria SA Anthony).

DSAEK was subsequently conducted according to the standardized technique described by Busin et al.[18] The unprepared corneal grafts were stored in organ culture in 2 regional tissue banks (the Besançon Franche-Comte and Nancy-Brabois Lorraine tissue banks) and were delivered in deturgescence and shipment medium (CORNEAJET, ref EYEJET00-1O; EUROBIO, Les Ulis, France) after 2 days of deturgescence. The CGT of the graft was first measured by using an ultrasound pachymeter (Handy Pachymeter SP-100; Tomey Corp, Nagoya, Japan). To obtain the thinnest possible posterior endothelial lamellar graft (thickness 70–220 μm), the graft was then thinned on an artificial chamber (Moria Single-Use Artificial Chamber, ref 19182; Moria SA) by using a rotational microkeratome with a 300- or 350-μm head (CBm turbine; Moria SA). The preoperative CGT of each graft was then measured with the same ultrasound pachymeter. The graft was subsequently trephined with a Hanna punch (One; Moria SA) to produce an 8-mm diameter section. A second corneal incision was made opposite the first incision, through which a pair of 23-gauge forceps (Single-Use Busin Forceps 23G No. 17301; Moria SA) was introduced. With constant irrigation, the graft was carefully placed on a Busin spatula (Single-Use Busin Spatula # 17300; Moria SA) and then introduced into the anterior chamber using Single-Use Busin Forceps. The graft was positioned centrally on the posterior surface of the recipient cornea by intracameral injection of a sterile air bubble. If necessary, corneal sutures were placed with nylon thread 10-0. Patients were instructed to adopt a supine position for the first 12 hours after surgery.

Postoperative Measurements

All patients underwent complete ophthalmological examinations 8 and 15 days and 1, 3, 6, and 12 months after surgery. Postoperative CGT was also measured at these time points by a specifically dedicated orthoptist, who applied AS-OCT while using calipers in the center of the graft at the echo location.

Statistical Analysis

The data, which were all recorded prospectively, were complete for all patients. Continuous and categorical data were expressed as mean ± SD or n (%), respectively. Patient groups were compared by using the Student *t* test, analysis of variance, or χ^2 test. Multivariate linear or logistic regression analysis with 95% confidence intervals (CIs) was used to identify clinical factors that associated with 12-month postoperative BSCVA or 6-month postoperative CGT. Correlation analyses were performed by determining the Pearson correlation coefficient. All analyses were performed with SAS/STAT software version 9.4 (SAS Inst, Cary, NC). The significance level was set to 0.05.

RESULTS

Characteristics of the Patients and Eyes in the Cohort

In total, 108 eyes (68 patients) were treated with DSAEK during the study period. Half (52%) of the patients had moderate PBK and the rest either had FECD (25%) or were receiving a second graft (23%). Two thirds of the patients were women, and the mean age was 76 years. Cystoid macular edema and graft rejection were almost nonexistent. Postoperative rebubbling was rare (6%). The surgical success rate (defined as a clear cornea with the graft in place and quantifiable visual acuity at 12 postoperative months) was 100% (Table 1).

After surgery, the DSAEK patients exhibited an initial decrease in BSCVA on day 8 that returned to preoperative levels on day 15 and then progressively improved over the next year to an average of 0.33 logarithm of the minimum

TABLE 2. Univariate Comparison of Eyes That Received Preoperative Thick (>130 μm) and Thin (≤130 μm) DSAEK Grafts for Demographic, Clinical, and Surgical Characteristics and BSCVA

Characteristics	Thick Preoperative DSAEK Graft (n=87)	Thin Preoperative DSAEK Graft (n = 21)	P*
Age, yr	76 ± 10	75 ± 9	0.57
Female sex	57 (66)	14 (67)	0.99
Indication			0.30
PBK	45 (52)	11 (52)	
FECD	24 (28)	3 (14)	
Second graft	18 (21)	7 (33)	
Triple procedure	6 (7)	2 (10)	0.65
First graft	65 (75)	13 (62)	0.28
Graft age, yr	67 ± 12	68 ± 13	0.87
Preop graft ECD, cells/mm^2	2489 ± 208	2569 ± 212	0.12
Operating time, min	33 ± 9	33 ± 7	0.73
Complications			
Cystoid macular edema	0 (0)	1 (5)	0.19
Rebubbling	4 (5)	3 (14)	0.13
CGT, μm			
Preoperative	180 ± 37	98 ± 18	**<0.001**
Day 8	150 ± 61	77 ± 22	**<0.001**
Day 15	132 ± 49	70 ± 19	**<0.001**
Month 1	122 ± 48	62 ± 16	**<0.001**
Month 3	116 ± 47	57 ± 13	**<0.001**
Month 6	115 ± 45	55 ± 14	**<0.001**
Month 12	115 ± 47	61 ± 13	**<0.001**
BSCVA			
Preoperative	0.98 ± 0.36	1.11 ± 0.41	0.12
Month 6	0.38 ± 0.15	0.4 ± 0.19	0.64
Month 12	0.33 ± 0.17	0.34 ± 0.17	0.73

The data are shown as mean ± SD or n (%). Statistically significant result with $P < 0.05$.
*χ^2 or Student t tests.
Preop, preoperative; triple procedure, phaco-DSAEK.

angle of resolution. The mean pachymetry-measured preoperative CGT was 164 μm. The postoperative OCT measurements showed that CGT dropped progressively after surgery until 3 months, at which point it plateaued at 103 to 105 μm (Table 1).

Comparison of the DSAEK-Operated Eyes That Had Thin and Thick Grafts Before Surgery

The eyes were then divided according to whether their preoperative CGT was thicker or thinner than 130 μm. In total, 87 eyes (62 patients) and 21 eyes (17 patients) were in the preoperative (denoted Pre for ease of reading) thick and thin graft groups, respectively. In other words, the eyes in the Pre thick graft group had undergone the conventional DSAEK procedure, whereas the eyes in the Pre thin graft group had undergone UT-DSAEK. The mean preoperative CGT in these groups was 180 ± 37 and 98 ± 18 μm, respectively ($P < 0.001$). The Pre groups did not differ significantly in any variable on univariate analysis except for postoperative CGT, which was significantly thicker in the Pre thick graft group at all time points (all $P < 0.001$). This suggests that there is a relationship between preoperative and postoperative CGT. Notably, the Pre groups did not differ in BSCVA before or at any time point after surgery (Table 2). Thus, in our hands, UT-DSAEK did not achieve better visual outcomes than conventional DSAEK.

TABLE 3. Univariate Comparison of Eyes That Had Postoperative Thick (>100 μm) or Thin (≤100 μm) DSAEK Grafts for Demographic, Clinical, and Surgical Characteristics and BSCVA

Characteristic	Postoperative Thick DSAEK Grafts (n = 50)	Postoperative Thin DSAEK Grafts (n = 58)	P*
Age, yr	76 ± 10	76 ± 9	0.71
Female sex	34 (68)	37 (64)	0.69
Indication			0.44
PBK	29 (58)	27 (47)	
FECD	10 (20)	17 (29)	
Second graft	11 (22)	14 (24)	
Triple procedure	2 (4)	6 (10)	0.28
First graft	38 (76)	40 (69)	0.52
Graft age, yr	69 ± 8	66 ± 14	0.16
Preop. graft ECD, cells/mm^2	2435 ± 208	2565 ± 194	**0.001**
Operating time, min	34 ± 9	33 ± 9	0.37
Complications			
Cystoid macular edema	0 (0)	1 (2)	0.99
Rebubbling	1 (2)	6 (10)	0.12
CGT, μm			
Preoperative	196 ± 42	137 ± 33	**<0.001**
Day 8	180 ± 64	98 ± 27	**<0.001**
Day 15	158 ± 47	87 ± 24	**<0.001**
Month 1	148 ± 47	78 ± 22	**<0.001**
Month 3	142 ± 45	72 ± 20	**<0.001**
Month 6	141 ± 42	70 ± 18	**<0.001**
Month 12	142 ± 45	72 ± 17	**<0.001**
BSCVA, logMAR			
Preoperative	0.96 ± 0.35	1.04 ± 0.39	0.31
Month 6	0.43 ± 0.15	0.34 ± 0.17	**0.007**
Month 12	0.38 ± 0.15	0.28 ± 0.17	**0.002**

The data are shown as mean ± SD or n (%). Statistically significant result with $P < 0.05$.
*χ^2 or Student t tests.
Preop, preoperative; triple procedure, phaco-DMEK or phaco-DSAEK.

TABLE 4. Multiple Linear Regression–Determined Ability of Factors to Predict 12-Month BSCVA, Including Preoperative DSAEK Graft Thickness

Variable	Parameter Estimates (95% CI)	*P*
Preop BSCVA	0.05 (−0.04 to 0.14)	0.29
Patient age	0.003 (−0.001 to 0.007)	0.06
Female sex	−0.02 (−0.09 to 0.05)	0.51
Indication		
FECD (ref)	—	—
PBK	0.02 (−0.08 to 0.09)	0.90
Second graft	−0.02 (−0.2 to 0.15)	0.85
First graft	0.01 (−0.15 to 0.15)	0.95
Graft age	−0.001 (−0.004 to 0.002)	0.51
Preop graft ECD	−0.0003 (−0.0005 to 0.0001)	**0.001**
Operating time	−0.001 (−0.004 to 0.003)	0.80
Cystic macular edema	0.25 (−0.10 to 0.61)	0.16
≥1 rebubbling session	0.08 (−0.05 to 0.22)	0.24
Patient groups		
Thick preop DSAEK graft* (ref)	—	—
Thin preop DSAEK graft*	0.02 (−0.06 to 0.10)	0.65

*Thick and thin preoperative grafts are defined as grafts that are >130 μm and ≤130 μm, respectively.
Preop, preoperative.
Statistically significant result with $P < 0.05$.

Comparison of the DSAEK-Operated Eyes That Had Thick and Thin Grafts at 6 Postoperative Months

The eyes were then divided according to whether their graft 6 months after surgery was thicker or thinner than 100 μm. In total, 50 eyes (30 patients) and 58 eyes (38 patients) were in the postoperative (denoted Post for ease of reading) thick and thin graft groups, respectively. Their mean CGT at 6 months was 141 ± 42 and 70 ± 18 μm, respectively ($P < 0.001$). The 2 groups did not differ significantly in any variable on univariate analysis except 1) preoperative ECD, which was significantly smaller in the Post thick graft group (2435 vs. 2565 cells/mm^2; $P = 0.001$); 2) postoperative CGT, which as expected was thicker at all time points in the Post thick graft group (all $P < 0.001$); and 3) preoperative CGT, which was significantly thicker in the Post thick graft group (196 vs. 137 μm; $P < 0.001$) (Table 3). Note that the last observation supports the notion advanced above, namely, that there is a relationship between preoperative and 6-month postoperative graft thickness.

The Post groups did not differ in BSCVA before surgery. Importantly, however, compared with the Post thick graft group, the Post thin graft group had significantly better BSCVA at 6 and 12 months ($P = 0.007$ and 0.002, respectively) (Table 3).

TABLE 5. Multiple Linear Regression–Determined Ability of Factors to Predict 12-Month BSCVA, Including 6-Month Postoperative DSAEK Graft Thickness

Variable	Parameter Estimates	*P*
Preop BSCVA	0.06 (−0.03 to 0.15)	0.16
Patient age	0.003 (−0.001 to 0.007)	0.06
Female sex	−0.03 (−0.09 to 0.04)	0.46
Indication		
FECD (ref)	—	—
PBK	0.001 (−0.78 to 0.78)	0.99
Second graft	−0.04 (−0.20 to 0.12)	0.63
First graft	−0.01 (−0.16 to 0.13)	0.88
Graft age	−0.001 (−0.004 to 0.002)	0.53
Preop graft ECD	−0.0002 (0.0004 to 0.0001)	**0.001**
Operating time	−0.0004 (−0.0041 to 0.0032)	0.81
Cystoid macular edema	0.28 (−0.05 to 0.62)	0.10
≥1 rebubbling session	0.11 (−0.02 to 0.24)	0.08
Patient groups		
Thick DSAEK graft at 6 mo* (ref)	—	—
Thin DSAEK graft at 6 mo*	−0.09 (−0.15 to −0.03)	**0.01**

*Thick and thin DSAEK grafts at 6 months are defined as grafts that are >100 and ≤100 μm, respectively.
Preop, preoperative.
Statistically significant result with $P < 0.05$.

Multivariate Analysis of Factors That Associate With BSCVA at 12 Months

The univariate analyses given in Tables 2 and 3 showed that although thin grafts at 6 postoperative months associated with better 12-month BSCVA than thick grafts at the same time point, this difference was not observed for the thick and thin preoperative grafts. To test whether these (non)associations were also observed on multivariate analysis, we conducted 2 linear regression analyses of the cohort. All preoperative/perioperative factors were included in both analyses. In addition, the first analysis included the Pre thick and thin graft groups (Table 4), whereas the second analysis included the Post thick and thin graft groups (Table 5). Both analyses found that greater preoperative ECD associated significantly with better 12-month BSCVA (*P* ranged from 0.04 to <0.001). Importantly, thin grafts at 6 months predicted better BSCVA at 12 months ($P = 0.01$) but thin preoperative grafts did not (Tables 4 and 5).

Multivariate Analyses of Factors That Associate With Postoperative Graft Thickness at 6 Months

We then conducted a third multivariate analysis to determine whether any preoperative/perioperative factors associated with postoperative thin grafts. The only factor that significantly predicted postoperative thin grafts was preoperative CGT ($P = 0.0003$) (Table 6). The Pearson correlation analysis also showed a strong correlation between preoperative and postoperative CGT ($r = 0.718$; $P < 0.0001$) (Fig. 1). This relationship was also observed when we analyzed the change in CGT over time for the Post and Pre groups (Fig. 2). Thus, the postoperative thin grafts started out and stayed significantly thinner than the postoperative thick grafts at all time points (all $P < 0.001$) (Fig. 2A). Moreover, the preoperative thin grafts continued to remain thinner at all postoperative time points than the preoperative thick grafts

TABLE 6. Multiple Logistic Regression–Determined Association of Factors That Predict 6-Month Postoperative Graft Thickness

Variable	Odds Ratio (95% CI)	*P*
Preop BSCVA	1.55 (0.2–11.79)	0.67
Patient age	1.03 (0.97–1.11)	0.30
Female sex	0.42 (0.09–2.07)	0.29
Indication		
FECD (ref)	—	—
PBK	0.18 (0.04–0.93)	0.64
Second graft	0.11 (0.01–7.25)	0.51
First graft	0.32 (0.01–20.93)	0.60
Graft age	0.99 (0.94–1.05)	0.69
Preop. graft ECD	1.003 (1–1.007)	0.06
Operating time	1.04 (0.95–1.13)	0.39
Preop CGT	0.91 (0.86–0.96)	**0.0003**
Rebubbling*	0.61 (0.04–10.04)	0.73

*Cystoid macular edema was not included in this analysis because of the paucity of events.
Preop, preoperative.
Statistically significant result with $P < 0.05$.

(all $P < 0.001$) (Fig. 2C). However, there was an interesting difference between the 2 groups when we examined the proportionate loss of thickness relative to preoperative thickness. Thus, the Post thin graft group lost more of their thickness over time (28%–49%) than the Post thick graft group (8%–28%) (Fig. 2B). By contrast, the Pre thick and thin Graft groups lost proportionately the same amount of thickness (17%–36% vs. 20%–44%) (Fig. 2D). These data suggest that something other than preoperative CGT is also influencing 6-month CGT and that this is the key factor that shapes final BSCVA.

It was notable that in the multivariate analysis shown in Table 6, preoperative ECD tended to predict 6-month graft thickness, although this association did not achieve statistical significance (odds ratio = 1.003, 95% CIs = 1–1.007; $P = 0.06$).

DISCUSSION

This study showed that 6-month postoperative DSAEK graft thickness, but not preoperative graft thickness, predicted better BSCVA at 12 months. This is consistent with, and further extends, the findings of our recent prospective study on 141 eyes with advanced PBK that underwent DSAEK[32]: this and the present study together show that postoperative CGT, but not preoperative CGT, plays a significant role in visual outcome over the long term in multiple DSAEK indications, namely, advanced PBK, moderate PBK, FECD, and second graft.

When taken at face value, our observation that preoperative CGT did not predict final BSCVA seems to contest the studies that have shown that this variable affects or correlates with final BSCVA after DSAEK.[18,20,21,31,36,37] For example, the randomized controlled trial of Dickman et al[20] shows quite convincingly that compared with conventional DSAEK with a mean (range) preoperative CGT of 209 (147–289) μm, UT-DSAEK with a mean CGT of 101 (50–145) μm significantly improved the 3-, 6-, and 12-month BSCVA in patients with FECD. However, there are also many other studies that, like us, did not find an association between preoperative CGT and final visual acuity after DSAEK.[28,30,32,35,38–41] It should be noted at this point that preoperative and postoperative CGT in DSAEK correlate, albeit variably, not just in this study (r = 0.72, $P < 0.0001$) but also our previous study (r = 0.85, $P < 0.001$)[32] and several other studies on DSAEK-CGT (r ranges from 0.59 to 0.90).[20,41–45] Therefore, we speculate that the discrepancies between studies in the relationship between preoperative CGT and final visual outcome may reflect interstudy variability in the accuracy of preoperative CGT measurements, which affects how well these measurements correlate with the more relevant clinical measure, namely, postoperative CGT.

Interstudy variability in preoperative CGT measurements could be due to differences in the way the grafts were prepared, such as whether they were precut versus being cut by the surgeon or organocultured versus kept in cold storage; although studies suggest these differences do not affect the

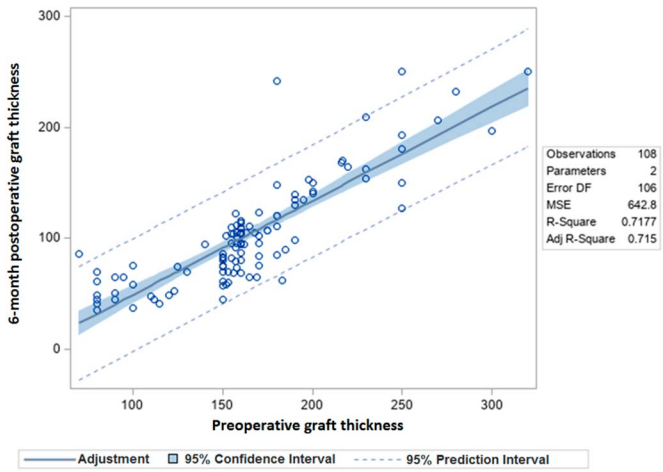

FIGURE 1. Correlation between preoperative and 6-month postoperative graft thickness, as determined by the Pearson correlation test (r = 0.718, $P < 0.0001$). (The full color version of this figure is available at www.corneajrnl.com.)

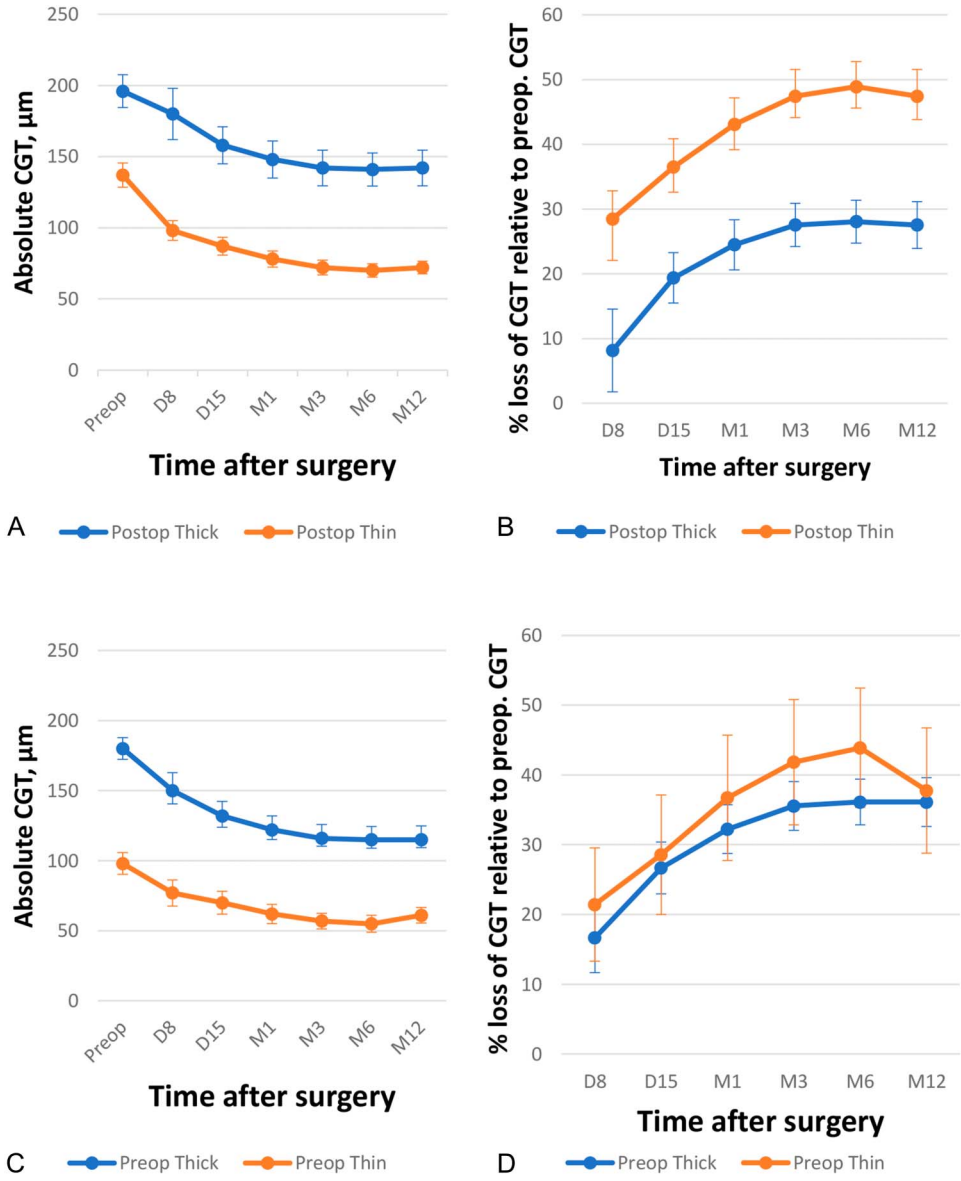

FIGURE 2. Change over time in CGT (A, C) and percentage loss of graft thickness relative to baseline (B, D) for grafts that were thick or thin 6 months after surgery (A, B) or thick and thin before surgery (C, D). Thick and thin grafts at 6 postoperative months were defined as CGT more or less than 100, respectively. Thick and thin preoperative grafts were defined as CGT more or less than 130 µm, respectively. The thick and thin grafts differed significantly from each other in all plots (all $P < 0.001$) except for D (P values ranged from 0.24 to 0.91), as determined by the Student t test. CGT, central graft thickness. (The full color version of this figure is available at www.corneajrnl.com.)

final visual acuity after DSAEK,[38,46–48] it is possible that they affect preoperative CGT measurements. For example, van Cleynenbreugel et al reported that thinner donor grafts may deturgescent slightly faster than thicker grafts[49]; thus, different deturgescence time frames could affect the distribution of preoperative graft thickness measurements and the relationship between this variable and final BSCVA. Another potential source of interstudy variability in preoperative CGT measurements is whether the CGTs were measured with US pachymetry or OCT: these methods correlate but not perfectly.[36,50–55] The longer duration between measurement by an eye bank technician versus the immediate measurement at the operating table by the surgeon could also contribute to interstudy variability in preoperative CGT measurements.

The notion that postoperative CGT, rather than preoperative CGT, is a better measure of a DSAEK graft's ability to restore visual acuity is supported by our comprehensive analysis of the literature. Many studies have been conducted on this question since 2009. When we focused on the randomized trials along with the retrospective/prospective studies with ~100 or more eyes, we found 6 studies that measured preoperative CGT alone and 4 studies (including this study) that measured both preoperative and postoperative CGT. The 6 preoperative CGT studies were all retrospective studies. Of these, 4 studies showed preoperative CGT had no effect on the visual acuity (see Supplemental Table S1, Supplemental Digital Content 1, http://links.lww.com/ICO/B299).[28,30,31,35,36,39] One of the 2 exceptions was the study by Gormsen et al[36]: they showed that eyes whose preoperative CGT was below the mean (111 µm) yielded slightly better BSCVA than the thicker preoperative grafts ($P = 0.04$). The other exception was the study by Terry et al,[31] who

showed that although preoperative CGT correlated significantly with BSCVA, it accounted for only 5% of the variation in BSCVA. This suggests that preoperative CGT plays at best a minor role in graft performance. Thus, none of these 6 studies show convincingly that preoperative CGT plays a significant role in final BSCVA. Of the 4 studies that measured both preoperative and postoperative CGTs, 2 studies were randomized trials: Interestingly, they showed that both CGT measurements correlated with BSCVA (see Supplemental Table S2, Supplemental Digital Content 1, http://links.lww.com/ICO/B299). The third and fourth were our own prospective/retrospective cohort studies, which showed that postoperative, but not preoperative, CGTs predicted better final visual acuity.[32] We speculate that the disparity of the randomized trials compared with our studies and the 6 studies on preoperative CGT may be due to the more regimented conditions in the trials, which may have led to more precise preoperative CGT measurements than we and others were able to achieve in routine clinical practice. The 2011 study by Neff et al, which precipitated the development of UT-DSAEK, should also be mentioned here. This study on 33 eyes was on postoperative (not preoperative) CGT and showed that when this variable was below 131 μm mean, the transplant associated with significantly better final BSCVA ($P < 0.01$).[16] Thus, although associations between preoperative CGT and final visual acuity have been noted occasionally, postoperative CGT seems to reflect visual outcomes more consistently. As discussed above, this pattern is possibly due to inaccuracies in preoperative CGT measurements and the correlation between preoperative and postoperative CGTs.

When we analyzed percentage change in CGT relative to baseline, which takes into account the correlation between preoperative and postoperative CGT, the preoperative thick and thin grafts thinned at similar rates. By contrast, the postoperative thin grafts exhibited significantly better thinning over time, starting from the time of the surgery, than the postoperative thick grafts. This suggests that a factor other than preoperative graft thickness is also influencing 6-month graft thickness and that this is a key factor that shapes final BSCVA. What is this factor? We speculate that it relates to the underlying endothelial healthiness of the graft, specifically the ability of the endothelium to reduce the hydration (and therefore thickness) of both graft and cornea. In particular, this "healthiness" factor may reflect the barrier and pump functions of the corneal endothelium that respectively control how much fluid enters and exits the corneal stroma.[56,57] It is possible that the endothelial cells in grafts that thin sharply after surgery restore stromal hydration more quickly than the endothelial cells in the grafts that remain thick. Notably, both barrier and pump functions of endothelial cells depend on ECD, which reflects the number of tight junctions between endothelial cells: The thinning of the endothelium with age or disease reduces these tight junctions, thus increasing the passive diffusion-type leakage of anterior chamber fluid into the stroma and decreasing the active removal of stromal fluid by Na^+/K^+-ATPase ion pumps.[57] Notably, in our study, we observed that higher preoperative ECD associated significantly with postoperative thin grafts on univariate analysis (Table 3) and tended to predict postoperative thin grafts on multivariate analysis (odds ratio = 1.003, 95% CIs = 1–1.007; $P = 0.06$) (Table 6). The latter lack of statistical significance may reflect the microkeratome preparation of the graft just before DSAEK or other preoperative/perioperative variables that could cumulatively or synergistically affect the preoperative ECD in the graft in unpredictable ways.[58,59] This notion is supported by several studies that show that although preoperative ECD does correlate with postoperative ECD after DSAEK, the correlation is weak (r values range from 0.184 to 0.39).[60–62] To address this question further, it would be of interest to determine the association between final BSCVA and early postoperative ECD or other measures of endothelial cell health such as cell size heterogeneity or hexagonality; however, it is difficult to make these measurements soon after DSAEK because of corneal edema, the increased thickness of the grafted cornea, and the stroma–stroma interface. Nonetheless, our data tentatively support the notion that intrinsic graft healthiness (potentially ECD) determines postoperative graft thinning and that this ultimately plays a key role in final BSCVA after DSAEK.

In summary, this study offers a possible explanation for the ongoing discrepancies in the field regarding the clinical relevance of DSAEK graft thickness: We suggest that because of preoperative/perioperative factors, preoperative CGT measurements can vary markedly between studies, leading some but not others to detect an association between preoperative CGT and final visual acuity. By contrast, postoperative CGT may predict postoperative BSCVA more reliably because it better reflects the intrinsic healthiness of the graft and therefore its ability to thin and improve the visual acuity. Further studies are needed to determine the preoperative factors that predict the ability of these grafts to thin after transplantation.

Study Limitations

This study had a number of limitations. First, it was a retrospective study, which could lend it to information and selection bias. However, this issue may be mitigated to some degree by the fact that the data were collected prospectively. Second, the sample size in the Pre thin group was limited (n = 21). This reflects difficulties in preparing very thin DSAEK grafts and the fact that thicker DSAEK grafts are easier to handle during surgery than thin ones.[49] However, when we used the mean preoperative CGT value (160 μm) of the DSAEK cohort as the threshold, the Pre thick and thin groups were more balanced (58 and 50, respectively), but nonetheless, the same results were obtained. Third, the study was conducted in a single center; thus, further studies in other centers or multicenter studies are needed to determine whether our findings are generalizable to other settings.

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