Published in final edited form as:

Am J Ophthalmol. 2011 December ; 152(6): 910–916. doi:10.1016/j.ajo.2011.05.003.

Graft Thickness, Graft Folds, and Aberrations after Descemet Stripping Endothelial Keratoplasty for Fuchs Dystrophy

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Abstract

Purpose—To determine whole eye high-order aberrations (HOAs) in pseudophakic eyes after Descemet stripping endothelial keratoplasty (DSEK) for Fuchs dystrophy, and to establish relationships between graft thickness, HOAs, and visual acuity.

Design—Cross-sectional study.

Methods—Whole eye HOAs were measured in pseudophakic eyes at intervals through 24 months after DSEK, and in otherwise healthy pseudophakic control eyes implanted with the same type of spherical intraocular lens. Wavefront errors were assessed by a Hartmann-Shack aberrometer over a 4 mm-diameter optical zone. In DSEK eyes, central graft thickness and stromal graft folds were measured by using confocal microscopy *in vivo*, and best-corrected visual acuity (BCVA) was determined by the electronic Early Treatment of Diabetic Retinopathy Study method.

Results—Total HOAs at 24 months after DSEK ($0.28 \pm 0.11 \mu\text{m}$, mean $\pm$ SD, $n=17$) were higher than those in pseudophakic controls ($0.16 \pm 0.07 \mu\text{m}$, $n=25$, $p<0.001$); specifically, trefoil and quadrafoil were higher after DSEK. At 24 months, total HOAs ($r=0.69$, $p<0.001$) and graft folds ($r=0.41$, $p=0.02$) were correlated with central graft thickness, and BCVA was correlated with total HOAs ($r=0.39$, $p=0.01$) but not with graft thickness ($r=-0.24$, $p=0.20$, $n=27$).

Conclusions—Whole eye HOAs are higher after DSEK compared to untreated corneas. Thicker grafts are associated with increased HOAs and more graft folds, suggesting that the donor lenticule contributes, in part, to the wavefront errors. Although BCVA is weakly related to total HOAs after DSEK, it is not related to graft thickness.

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Financial Disclosures: None (all authors)

Contributions of authors in each of these areas: Design of the study (JWM, KHB, SVP); conduct of the study (LSS, CBN, JWM, KHB, SVP); collection (LSS, CBN, KHB, SVP); management (LSS, CBN, JWM, SVP); analysis (JWM, KHB, SVP); and interpretation (LSS, JWM, KHB, SVP); of the data; preparation (LSS, JWM, SVP); review (LSS, CBN, JWM, KHB, SVP); and approval (LSS, CBN, JWM, KHB, SVP) of the manuscript

Statement about Conformity with Author Information: This study was approved by the Mayo Clinic Institutional Review Board and complied with the Health Insurance Portability and Accountability Act. Informed consent was obtained from all subjects.

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INTRODUCTION

Descemet stripping endothelial keratoplasty (DSEK) is currently the preferred technique of corneal transplantation for endothelial disease. The success and rapid adoption of this technique can be attributed to distinct advantages over penetrating keratoplasty (PK), including better uncorrected visual acuity, more predictable postoperative refractive errors, and improved globe integrity.¹⁻³ In addition, graft survival, which is the standard measure of success for corneal transplantation,⁴ at 5 years is similar to that after PK, and endothelial cell loss appears to be lower.⁵ Despite these advantages, quality of vision often remains degraded compared to normal⁶ with best corrected visual acuity often being less than 20/20,^{3,7} and disability glare being higher than normal.^{1,6} In fact, poor vision after DSEK has been suggested to be a leading cause of graft replacement during the first five postoperative years.⁵

After DSEK for Fuchs dystrophy, we found that the large and small angle domains of the point-spread function were degraded compared to otherwise normal pseudophakic eyes.⁶ Degradation of the large angle domain was expected because of increased forward scatter that causes disability glare, whereas degradation of the small angle domain suggested that increased high-order aberrations (HOAs) might also degrade visual function after DSEK. In this study, we examined HOAs directly in DSEK patients; the goal of this study was to compare whole-eye HOAs in pseudophakic eyes after DSEK to those of age-matched, otherwise normal pseudophakic eyes implanted with the same type of spherical intraocular lens. We also assessed the relationships between HOAs, visual acuity, graft thickness, and stromal graft folds detected by confocal microscopy *in vivo*. Graft folds appear as dark striae in confocal images of the deep stroma, and may indicate a mechanical irregularity in the stroma that affects the curvature of the posterior corneal surface. Thus, in this study, we tested the hypothesis that thicker grafts were associated with more graft folds and increased HOAs.

METHODS

Subjects

Subjects in the DSEK group were part of a prospective, observational study of DSEK for Fuchs dystrophy^{1,8} and were recruited from patients attending the Department of Ophthalmology at Mayo Clinic, Rochester, Minnesota. Subject age was 67 ± 10 years (mean $\pm$ standard deviation; range: 41–87 years), and all eyes were pseudophakic after DSEK with the graft prepared by a mechanical microkeratome. Forty-six eyes (40 subjects) were examined at 6 months, 36 eyes (29 subjects) were examined at 12 months, and 27 eyes (24 subjects) were examined at 24 months after DSEK.

Data from eyes in the DSEK group were compared to data from eyes of subjects in two control groups. The first control group included 25 pseudophakic but otherwise normal eyes of 17 subjects at 5 ± 11 months (range: 1–60 months) after cataract surgery, and was age-matched to the DSEK group (70 ± 7 years; range: 55–83 years). The pseudophakic eyes were implanted with the same type of spherical intraocular lens (Acrysof SA60AT, Alcon Laboratories Inc., Fort Worth, TX) as in the DSEK group, and were controls for whole eye HOAs. The second control group included 36 young normal, untreated eyes of 18 subjects who had undergone confocal microscopy as part of another study⁹ and served as controls for graft folds; age was 43 ± 7 years (range: 29–55 years).

Subjects were excluded if they had corneal scarring or disease (except for haze related to Fuchs dystrophy in the DSEK group), diabetes, glaucoma, significant vitreous floaters, or if

their vision was impaired because of maculopathy, optic neuropathy, or amblyopia. Pseudophakic eyes were excluded if they had posterior capsular haze.

Surgical Procedures

The technique for DSEK has been described previously^{1,8} and involved a 5–6 mm sutured scleral tunnel incision, and 3–4 full-thickness host, paracentral corneal venting incisions. All grafts were prepared by using a mechanical microkeratome; grafts were inserted into the anterior chamber by using a folding technique. When cataract surgery was performed in combination with DSEK, the same scleral incision was used for cataract removal by phacoemulsification and for intraocular lens insertion. Of the 46 eyes examined at 6 months, 38 eyes had undergone simultaneous DSEK and phacoemulsification, whereas 8 eyes had undergone DSEK alone after previous phacoemulsification.

Pseudophakic eyes in the control group received cataract extraction by phacoemulsification and intraocular lens insertion through a 2.75 to 3 mm clear corneal, sutureless incision. All surgeries were uncomplicated and were without significant postoperative corneal edema.

Ocular aberrations

Whole eye HOAs were measured by using a Hartmann-Shack aberrometer (VISX WaveScan, Santa Ana, CA). Subjects self-fixated on a target within the aberrometer during wavefront acquisition. The highest quality examination with the largest wavefront (pupil) diameter, as determined by the software, was selected by one masked observer (LSS). Wavefront errors were calculated by using VOLCT (Sarver and Associates Inc, Carbondale, IL) over a 4-mm optical zone, and were decomposed into Zernike polynomials to the sixth order. The root mean square (RMS) of all aberrations in orders 3 through 6 were calculated from the Zernike coefficients, as were the RMS of spherical aberration (Z_4^0), coma (Z_3^{-1}, Z_3^1), trefoil (Z_3^{-3}, Z_3^3), and quadrafoil (Z_4^{-4}, Z_4^4). Aberrometry was attempted in only 23 eyes at 6 months, 31 eyes at 12 months, and 24 eyes at 24 months after DSEK, and in all pseudophakic control eyes.

Confocal Microscopy and Graft Folds

Central corneas were examined by using a confocal microscope (ConfoScan 4 with z-ring adapter, Nidek Technologies, Freemont, CA) to measure graft thickness and folds in eyes after DSEK, and to measure deep stromal folds in the young, normal corneas. The microscopy technique has been described in detail previously.¹⁰ The best full-thickness scan through the cornea was selected for analysis, and graft thickness was calculated by using the graph of intensity of the confocal images through the cornea.⁸

Graft folds were assessed from confocal images by one masked observer (CBN). In each image, all folds that were visible within a central rectangle (215 $\mu\text{m} \times 242 \mu\text{m}$; area, 0.052 mm^2) were identified and marked by using a point-and-click method (Figure 1). This region of the confocal image had the most consistent brightness, and visibility of folds decreased outside of this area. Folds were marked only once in any frame but were marked again if they appeared in consecutive frames. The folds index was the sum of the number of folds per frame (weighted for the distance, registered by the z-ring adapter, between consecutive frames) between the interface and the endothelium after DSEK, or between the endothelium and 160 μm , (the mean central graft thickness after DSEK) anterior to the endothelium in untreated corneas.

Other Outcome Measures

Best-spectacle corrected high-contrast visual acuity (BCVA) was measured by using the electronic Early Treatment of Diabetic Retinopathy Study protocol.¹¹ Letter scores were converted to logarithm of the minimum angle of resolution (log MAR).

Statistical Analysis

Data were reported for the DSEK group at 6, 12 and 24 months after surgery. Aberrations and folds indices were compared between the DSEK and control groups, and over time within the DSEK group, by using generalized estimating equation (GEE) models to account for possible correlation between fellow eyes of the same subject.¹² P-values were adjusted for multiple comparisons by using the Bonferroni method, and $p \leq 0.05$ was considered statistically significant. Correlations were assessed by the Pearson correlation coefficient with significances assessed by using GEE models.

RESULTS

High-order aberrations

The aberrometer could not acquire wavefront errors in 8 of 23 eyes at 6 months, in 8 of 31 eyes at 12 months, and in 4 of 24 eyes at 24 months after DSEK. In addition, aberrometry could not be used in 2 eyes at 6 months, 2 eyes at 12 months, and 3 eyes at 24 months because the measured pupil diameter was less than the desired wavefront diameter (4 mm). Thus, aberrometry data were available for 13 eyes at 6 months, 21 eyes at 12 months, and 17 eyes at 24 months.

Total HOAs were higher at 6, 12 and 24 months after DSEK than those of otherwise normal pseudophakic controls (Table 1, Figure 2), specifically with higher trefoil and quadrafoil at every examination (Table 1, Figure 2). Coma was higher at 24 months after DSEK than in pseudophakic controls ($p=0.04$, Figure 2). There were no differences in HOAs between 6, 12 and 24 months after DSEK.

Total HOAs were not correlated with graft thickness at 12 months after DSEK ($r=0.24$, $p=0.41$, $n=19$; Figure 3), but were correlated with graft thickness at 24 months ($r=0.69$, $p<0.001$, $n=15$; Figure 3). At 24 months, graft thickness was correlated with coma ($r=0.60$, $p<0.001$, $n=15$), trefoil ($r=0.57$, $p<0.001$, $n=15$), and quadrafoil ($r=0.57$, $p<0.001$, $n=15$). Graft thickness data were reported previously.⁸

At 12 months after DSEK, BCVA was not correlated with total HOAs ($r=0.25$, $p=0.10$, $n=21$; Figure 4), but was correlated with quadrafoil ($r=0.61$, $p<0.001$, $n=21$). At 24 months after DSEK, BCVA was correlated with total HOAs ($r=0.39$, $p=0.01$, $n=17$; Figure 4), trefoil ($r=0.38$, $p<0.001$, $n=17$), and quadrafoil ($r=0.49$, $p<0.001$, $n=17$). BCVA did not correlate with graft thickness at 12 months ($r=-0.08$, $p=0.57$, $n=36$) or 24 months ($r=-0.24$, $p=0.20$, $n=27$) after DSEK.

Graft Folds

Stromal folds were visible in all grafts examined at 6, 12, and 24 months after DSEK, and the folds index did not change with time (Table 2). Deep stromal folds were also visible in 34 of 36 untreated, normal corneas. The folds index at each examination after DSEK was higher than in the same thickness (160 μm) of corresponding deep stroma of controls (Table 2).

The folds index was correlated with graft thickness at 12 months ($r=0.27$, $p=0.03$, $n=36$; Figure 5) and 24 months ($r=0.41$, $p=0.02$, $n=27$; Figure 5) after DSEK, and with total

HOAs at 24 months ($r = 0.44$, $p = 0.003$, $n = 15$). The folds index was not correlated with total HOAs at 12 months after DSEK ($r = 0.34$, $p = 0.06$, $n = 19$), or with BCVA at 12 months ($r = 0.02$, $p = 0.90$, $n = 36$) or 24 months ($r = 0.08$, $p = 0.66$, $n = 27$) after DSEK.

DISCUSSION

High-order aberrations are higher in pseudophakic eyes after DSEK compared to age-matched otherwise healthy pseudophakic controls implanted with the same type of spherical intraocular lens. At 24 months after DSEK, there was a strong association between increased HOAs and thicker grafts, and a weaker association between increased HOAs and decreased BCVA.

High-order aberrations are the primary source of decreased visual acuity after penetrating keratoplasty,^{13,14} with the irregular anterior corneal surface¹⁵ being a major contributor to the aberrations because of the large difference in refractive index between air and cornea. In contrast, because the anterior corneal surface is minimally disturbed during DSEK, one would expect minimal induction of whole eye HOAs, yet we found that these were significantly increased compared to controls, even at 2 years after surgery. In fact, ocular HOAs after DSEK in this study were higher than those after non-wavefront-guided LASIK in a concurrent study using the same instrument and methods¹⁶; although the age and lenticular status of the LASIK and DSEK groups were different and prevented a fair comparison, the data indicate that HOAs after DSEK are important. The dominant HOAs at every examination after DSEK were trefoil and quadrafoil. We are unaware of other studies that have compared ocular aberrations between DSEK and controls, but ocular aberrations have been compared between endothelial keratoplasty and PK. Hindman et al. found that total HOAs were higher after PK than after deep lamellar endothelial keratoplasty,¹³ and Bahar et al. stated that ocular HOAs were higher after PK than after DSEK, although the differences in their study were not statistically significant.¹⁷ Although the incision length and location was different between the DSEK and pseudophakic control groups in our study, it is unlikely that this explained the difference in HOAs between these groups. Corneal incisions for cataract surgery are associated with only small increases in corneal HOAs,¹⁸ and scleral incisions induce fewer HOAs than corneal incisions.¹⁹ If the difference in aberrations was simply a result of different incisions, we would have expected our results to be opposite to what we found with lower aberrations in the DSEK eyes (scleral incision) than in the pseudophakic control (corneal incision) eyes.

Given the minimal disruption of the anterior corneal surface during DSEK, the posterior corneal (graft) surface is a likely source of increased HOAs. Muftuoglu et al. found that aberrations from the posterior corneal surface after DSEK were higher than in controls, although they were not significantly different from those after PK.²⁰ Yamaguchi et al. also did not find a difference in posterior corneal irregularity between DSEK and PK.²¹ We did not directly measure the aberrations derived from the posterior corneal surface in this study, but we did examine relationships between the posterior lamellar graft and whole eye aberrations. We found that coma, trefoil, and quadrafoil increased with thickness of grafts at 24 months, and that thicker grafts were associated with more graft folds. These data indirectly suggest that the posterior graft surface is a source of increased aberrations after DSEK. Nevertheless, the contribution of the anterior corneal surface to ocular aberrations should not be ignored after DSEK. Although irregularities of the anterior surface are lower after endothelial keratoplasty than they are after PK,^{15,21} they might significantly contribute to increased whole eye aberrations because of the large change in refractive index at the anterior corneal surface. In fact, Yamaguchi et al. found that BCVA after DSEK correlated with anterior corneal irregularity and not posterior corneal irregularity,²² and although Muftuoglu et al. did not find a statistical difference between anterior corneal aberrations

after DSEK compared to controls, their data indicated a trend toward increased aberrations in the DSEK group.²⁰

The relationship between HOAs and graft thickness was variable; it was significant at 24 months after DSEK but not at 12 months. This could be explained by a change in the configuration of the donor lenticule between 1 and 2 years after surgery, particularly if the periphery of the donor thinned more slowly than the center. Alternatively, central graft thickness might not be as important as the mismatch in curvature between the anterior surface of the donor and the posterior surface of the host with respect to irregularity of the posterior graft surface, and thus in some cases, posterior surface irregularity could be independent of central graft thickness. Although thicker grafts were associated with increased aberrations at 24 months, they were not associated with decreased BCVA at 24 months, consistent with our findings at 12 months.⁸ The predictive relationship between HOAs and BCVA was weak ($\approx 15\%$ from r^2) and was mainly evident at 24 months after DSEK, and this can be explained by the dominant aberrations after DSEK being trefoil and quadrafoil, which have a lesser effect on visual acuity compared to aberrations such as spherical aberration.^{23,24} Nevertheless, because different combinations and magnitudes of aberrations have variable effects on visual acuity, individual eyes can vary widely from the mean and therefore some eyes might suffer from decreased acuity because of the donor lenticule. Indeed, poor vision after DSEK was a leading cause of graft replacement in one series,⁵ and graft replacement was associated with improved visual acuity in most of those cases.²⁵

Graft folds were present in all eyes examined by confocal microscopy at 2 years after DSEK. However, we also detected folds in confocal images of the deep stroma of most of the untreated normal corneas, and we attributed this to pressure exerted on the cornea by the ConfoScan z-ring. While we cannot rule out that some folds in the DSEK grafts were also induced by the z-ring, there were more folds in DSEK eyes than there were in the normal eyes, and they were associated with graft thickness and HOAs; this suggests that not all the folds were an artifact of examination. Indeed, folds were visible in confocal images of some DSEK corneas (not included in this study) that were examined without the z-ring. With careful slit-lamp examination at high-magnification, subtle stromal microfolds are visible in healthy DSEK grafts and they appear similar to microfolds in LASIK flaps.²⁶ These graft microfolds are present in most DSEK grafts, and are distinct from macrofolds, which are visible at lower magnification, and are known to impair vision.^{25,27} The deep stromal folds in the DSEK grafts were probably the result of a subtle mismatch in curvature between the posterior surface of the host stroma and the anterior surface of the graft, and might have contributed to irregularity of the posterior surface of the graft. Unfortunately, a comprehensive quantitative analysis of graft folds was not possible without use of the z-ring during confocal microscopy, because the z-ring was required for stabilizing the cornea and for accurate corneal depth measurements.¹⁰

The presence of more than normal folds should be interpreted with caution because of the possible influence of the z-ring adapter, as discussed above, and because folds were measured in a very small area ($215\ \mu\text{m} \times 242\ \mu\text{m}$) of the central cornea, which might not have been representative of the entire optical zone. In addition, no precedent has been set for the best method of quantifying stromal folds in a volume of tissue. We determined a folds index, which was not a true absolute number or density of folds, but which combined the number of folds per frame with the distance the folds extend through the stroma (repeated identification in consecutive frames). By weighting each frame for the unequal distance between frames, and by summing all appearances of a fold through multiple frames, the folds index may have better reflected the effect of folds on vision; a fold that extended

through a distance was likely to have a greater effect than a fold that extended through half that distance.

This study was limited by the small number of eyes after DSEK that were measurable by our aberrometer. Although it is possible that the eyes in which wavefront data could not be acquired had very degraded optical properties, which could bias the analysis, the BCVA of the eyes in which wavefront data were obtained at 12 months (0.17 ± 0.15 log MAR, $n=23$) was similar to that of eyes in which wavefront data could not be obtained (0.20 ± 0.16 log MAR, $n=8$, $p=0.62$). This implies that eyes in which wavefront errors could not be measured did not have very degraded optical properties.

In summary, ocular HOAs were significantly higher in pseudophakic eyes after DSEK for Fuchs dystrophy than in otherwise healthy pseudophakic eyes. Thicker grafts were associated with more graft folds and with increased HOAs, but the average effect of the HOAs on visual acuity was small. Nevertheless, because individual eyes vary from the mean, the donor lenticule can be a source of decreased vision in some cases after DSEK.

Acknowledgments

Funding/Support: Supported by Research to Prevent Blindness, Inc., New York, NY (an unrestricted departmental grant, and SVP as Olga Keith Wiess Special Scholar); Mayo Clinic Center for Translational Science Activities Grant Number UL1 RR024150 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH); and Mayo Foundation, Rochester, MN.

Other Acknowledgments: Statistical expertise was provided by David O. Hodge, Department of Health Sciences Research, Mayo Clinic, Rochester, MN.

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Figure 1.

Graft folds after Descemet stripping endothelial keratoplasty (DSEK).

Confocal microscopy image showing folds (dark striations) in the stroma of a healthy graft at 24 months after DSEK; the bright objects represent donor keratocyte nuclei. For quantification of folds, individual folds were marked (white x) only once in any frame but were marked again if they appeared in consecutive frames. The folds index was the sum of the number of folds per frame (weighted for the distance between consecutive frames) between the interface and the endothelium after DSEK, or between the endothelium and 160 μm anterior to the endothelium in untreated corneas.

Figure 2. High-order aberrations (HOAs) after Descemet stripping endothelial keratoplasty (DSEK). Total HOAs were higher in pseudophakic eyes at 24 months after DSEK compared to otherwise normal pseudophakic eyes implanted with the same type of spherical intraocular lens. At 24 months, coma, trefoil, and quadrafoil were higher after DSEK than in the controls.

Figure 3.

Relationship between graft thickness and ocular high-order aberrations (HOAs) after Descemet stripping endothelial keratoplasty (DSEK).

Total HOAs were not correlated with graft thickness at 12 months after DSEK ($r = 0.24$, $p = 0.41$, $n = 19$), but were correlated with graft thickness at 24 months ($r = 0.69$, $p < 0.001$, $n = 15$).

Figure 4.

Relationship between ocular high-order aberrations (HOAs) and best-corrected visual acuity (BCVA) after Descemet stripping endothelial keratoplasty (DSEK).

BCVA was not correlated with total HOAs at 12 months after DSEK ($r=0.25$, $p=0.10$, $n=21$), but was correlated with total HOAs at 24 months ($r=0.39$, $p=0.01$, $n=17$).

Figure 5.

Relationship between graft thickness and graft folds after Descemet stripping endothelial keratoplasty (DSEK).

The folds index was correlated with graft thickness at 12 months ($r = 0.27$, $p = 0.03$, $n = 36$) and 24 months ($r = 0.41$, $p = 0.02$, $n = 27$) after DSEK.

High-order aberrations in pseudophakic eyes after Descemet stripping endothelial keratoplasty (DSEK), and in otherwise normal pseudophakic eyes.

Table 1

	Wavefront Error (4 mm-diameter optical zone), RMS (μm) (P-value ^d)				
	Total High-Order Aberrations	Spherical Aberration	Coma	Trefoil	Quadrafoil
DSEK					
6 months (n=13)	0.26 $\pm$ 0.07 (<0.001)	0.07 $\pm$ 0.06 (0.99)	0.10 $\pm$ 0.05 (0.87)	0.17 $\pm$ 0.07 (<0.001)	0.07 $\pm$ 0.04 (<0.001)
12 months (n=21)	0.25 $\pm$ 0.08 (<0.001)	0.10 $\pm$ 0.06 (0.93)	0.10 $\pm$ 0.06 (0.99)	0.18 $\pm$ 0.07 (<0.001)	0.07 $\pm$ 0.04 (<0.001)
24 months (n=17)	0.28 $\pm$ 0.11 (<0.001)	0.08 $\pm$ 0.05 (0.99)	0.15 $\pm$ 0.09 (0.04)	0.17 $\pm$ 0.07 (<0.001)	0.09 $\pm$ 0.06 (<0.001)
Pseudophakia ^{a,b} (n=25)	0.16 $\pm$ 0.07	0.07 $\pm$ 0.03	0.09 $\pm$ 0.07	0.08 $\pm$ 0.04	0.03 $\pm$ 0.02

^a P-values compare DSEK to pseudophakia; generalized estimating equation models with Bonferroni adjustment for 3 comparisons.

^b Implanted with the same type of spherical intraocular lens as in the DSEK group.

Table 2

Stromal folds in the graft after Descemet stripping endothelial keratoplasty (DSEK), and in the deep stroma of normal corneas.

	Folds Index (folds-μm)^a
DSEK	
6 months (n=46)	347 ± 174^b
12 months (n=36)	308 ± 122^c
24 months (n=27)	348 ± 148
Normal, untreated corneas (n=36)	200 ± 144^d

^aThe folds index was the sum of the number of folds per confocal image (weighted for the distance between consecutive images) between the interface and the endothelium after DSEK, or between the endothelium and 160 μm anterior to the endothelium in untreated corneas.

^bp=0.30 versus 12 months, p=0.99 versus 24 months

^cp=0.24 versus 24 months

^dp<0.001 versus DSEK at any examination