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Descemet membrane endothelial keratoplasty: graft rejection, failure and survival

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CHAPTER 7

360-Degree Scheimpflug Imaging to Predict Allograft Rejection after Descemet Membrane Endothelial Keratoplasty

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ABSTRACT

Purpose: To describe the use of 360-degree Scheimpflug imaging as a diagnostic tool for detection and documentation of subtle corneal changes preceding upcoming allograft rejection after Descemet membrane endothelial keratoplasty (DMEK).

Methods: A total of 17 eyes (16 patients) were diagnosed with clinically manifest allograft rejection 2 to 42 months after DMEK. 360-degree Scheimpflug images of consecutive follow-up examinations (from 3–60 months) of "asymptomatic" eyes before, during, and after rejection were retrospectively analyzed, to determine which abnormalities could be detected before allograft rejection became clinically manifest. The images were compared with DMEK control eyes (without rejection episode).

Results: Scheimpflug images at the time of rejection showed keratic precipitates as distinct retrocorneal nodular elevations and/or a significant increase in pachymetry of ≥7%. More subtle changes could be identified retrospectively in 9/17 eyes (53%) on an average at 8 (±5) months before rejection became clinically manifest; in all eyes, these subtle changes were not recognized at routine slit-lamp examinations by various ophthalmologists as inflammatory changes heralding allograft rejection. Secondary graft failure occurred in 4/17 eyes (24%). None of the control eyes showed relevant abnormalities with Scheimpflug imaging.

Conclusions: By screening the posterior corneal surface with 360-degree Scheimpflug imaging, subtle inflammatory retrocorneal deposits can be detected and recorded during consecutive follow-up visits. Hence, Scheimpflug imaging may have the potential to become a diagnostic tool for early detection of upcoming allograft rejection in asymptomatic DMEK eyes, that is, before the immune response becomes clinically manifest and before substantial endothelial cell damage occurs.

INTRODUCTION

Allograft rejection is one of the main complications after keratoplasty, potentially leading to secondary graft failure.[1,2] With the transition from full-thickness to lamellar grafting, the incidence of rejection has been reported to decline from 10% to 15% in penetrating keratoplasty (PK), to 5%–10% in Descemet-stripping (automated) endothelial keratoplasty (DSEK/DSAEK), to 1%–2% in Descemet membrane endothelial keratoplasty (DMEK).[1,3–11]

Recently, we described that specular microscopy image analysis may allow for detection of upcoming allograft rejection after DMEK because specific changes in endothelial cell morphology may precede allograft rejection.[12] Because these endothelial cell changes may be expected to be associated with other morphologic changes of the cornea, we hypothesized that Scheimpflug imaging and pachymetry could potentially reveal additional corneal changes that herald allograft rejection after DMEK.

Hence, the aim of the study was to assess corneal changes in 360-degree Scheimpflug images and pachymetry readings of consecutive follow-up visits taken from asymptomatic DMEK eyes that later developed a clinically manifest, that is, proven, allograft rejection and to compare the findings with those of DMEK control eyes (without a later rejection episode), to define additional screening parameters next to endothelial cell morphology changes.

MATERIALS AND METHODS

From a series of 750 consecutive DMEK eyes (570 patients operated on between 2006 and 2014, with a mean follow-up time of 51 [±23] months [range: 12–111 months]), 17 eyes of 16 patients (mean age 65 [±14] yrs) that developed a clinically manifest allograft reaction were enrolled in our retrospective study. These eyes underwent surgery for Fuchs endothelial corneal dystrophy (n = 12), pseudophakic bullous keratopathy (n = 1), bullous keratopathy for phakic intraocular lens removal (n = 2) and in the presence of a glaucoma drainage device (n = 1), or for failed DSEK (n = 1) and developed clinically manifest allograft rejection 2 to 42 months after surgery (mean follow-up after DMEK 35 (±15) months, range 9–60 months) (Table 1). None of these eyes had a history of infectious or noninfectious uveitis before DMEK and/or systemic immune disease.

Table 1. Demographics of rejection and control eyes after Descemet Membrane Endothelial Keratoplasty

	Study eyes (allograft rejection)	Control eyes (no allograft rejection)
Eyes / Patients (n)*	17/16	34/34
Mean age (years) ± SD (range)	65±14 (31-80)	66±12 (38-83)
Gender (male/female)	10/6	20/14
Pseudophakic / phakic	12/5	24/10
Preoperative diagnosis		
Fuchs endothelial corneal dystrophy	12	27
Bullous keratopathy	4**	5†
Re-graft (Failed DSEK)	1	2
Mean donor age (years) ± SD (range)*	63±10 (48-81)	63±7 (48-74)
Mean follow-up time (months) ± SD, (range)	35±15 (9-60)	47±12 (18-60)

* The study group and control group did not differ significantly ($P > .05$).
**Bullous keratopathy in the presence of a glaucoma tube (n=1), after phakic intraocular lens removal (n=2) and pseudophakia (n=1).
†Bullous keratopathy for radial keratotomy/laser in situ keratomileusis (n=1), for pseudophakia with an anterior (n=1) or posterior chamber lens (n=1) and for phakic intraocular lens removal (n=2).
SD = Standard deviation; DSEK = Descemet stripping endothelial keratoplasty.

From the same cohort, 34 asymptomatic eyes of 34 patients (matched for age, sex, lens status, and surgical indication) with a mean age of 66 (±12) years served as a control group; none of these had a history of allograft rejection or uveitis (Table 1).

The study was approved by the institutional review board of the Netherlands Institute for Innovative Ocular Surgery. All patients signed institutional review board–approved informed consent for research participation. The study adhered to the Declaration of Helsinki.

Rejection Episode

Graft rejection was defined as an event at which objective clinical findings were observed on slit-lamp examination (with or without subjective complaints). These included an endothelial rejection line, keratic precipitates with or without an increase in corneal thickness, anterior uveitis, and/or ciliary injection.

Donor Tissue

The procedure for harvesting a DMEK graft has previously been described.[13,14] In short, corneo-scleral buttons were excised from donor globes ≤36 hours post-mortem and stored in organ culture medium (CorneaMax; Eurobio, Courtaboeuf,

France) at 31°C. Endothelial cell morphology and viability were evaluated, and corneo-scleral buttons were mounted endothelial side up on a custom-made holder. A 9- to 10-mm diameter Descemet sheet with its endothelium was removed from the posterior stroma with the corneo-scleral rim immersed in balanced salt solution. Owing to elastic tissue properties, a "Descemet roll" formed spontaneously, with the endothelium on the outer side. Average donor age was 63 (±10) years for the study group and 63 (±7) years for the control group (Table 1).

Surgery

The DMEK surgical procedure has previously been described.[15] In short, a circular 9.0-mm diameter "descemetorhexis" was performed with complete air fill of the recipient's anterior chamber, by scoring and stripping off Descemet membrane from the posterior stroma with a reversed Sinskey hook (DORC International, Zuidland, the Netherlands). In the eye that underwent DMEK as a secondary procedure, the primary DSEK graft was carefully removed from the recipient's posterior stroma using a reversed Sinskey hook in an anterior chamber filled with air.

The donor Descemet roll was then stained (0.06% Trypan blue solution, VisionBlue, DORC International), sucked into a custom-made injector (Melles DMEK injector, DORC International) and injected through a 3.0-mm limbal tunnel incision into the recipient's anterior chamber. The graft was oriented with the endothelial side facing the recipient's iris, and Descemet membrane facing recipient's posterior stroma. After complete graft unfolding over the iris, a large air bubble was injected underneath the graft to position it onto the recipient's posterior stroma. The anterior chamber was then completely filled with air for 60 minutes followed by an air–liquid exchange leaving a 30%–50% air bubble in the anterior chamber.

At the end of surgery, subconjunctival dexamethasone and gentamicin were injected. Postoperative medication included antibiotic eye drops for 2 weeks, and a steroid regimen of dexamethasone 0.1% drops, 4 times daily for 4 weeks, followed by fluorometholone drops, 4 times daily tapered to once daily at 1 year postoperatively, and once daily or once every other day thereafter.[16]

Measurements

All study and control eyes were routinely examined before surgery, and postoperatively at 1, 3, 6, 9, and 12 months, and at 6-month intervals thereafter. Sequential images of pachymetry and high-resolution rotating Scheimpflug imaging (Pentacam; Oculus, Wetzlar, Germany) and slit-lamp photography (Topcon Medi-

cal Europe BV, Capelle a/d IJssel, the Netherlands) were evaluated retrospectively between 3 and 60 months postoperatively, in an attempt to detect corneal changes previously unrecognized.

For each measurement, the Scheimpflug camera generates 25 images over 360 degrees to produce a 3-dimensional image. For each study and control eye, all 25 Scheimpflug scans taken along the same meridian were compared between consecutive follow-up points to evaluate changes in the corneal posterior surface by 2 masked observers.

Changes in central corneal thickness were evaluated using differential pachymetry maps generated by Pentacam software. For all 17 eyes, Scheimpflug images and central corneal thickness before and after rejection were available, and in 11 eyes, reliable Scheimpflug images were also available at the time of rejection.

Statistical Analysis

An unpaired t test was performed for comparison of the study and control groups. $P < 0.05$ was considered statistically significant.

RESULTS

From a total of 750 DMEK eyes, 17 eyes developed allograft rejection on an average of 18 (±13) months (range: 2–42 months, median: 18 months) after surgery. One patient had allograft rejection in both eyes.

Scheimpflug Images and Pachymetry Findings Before Allograft Rejection Became Clinically Manifest

In retrospect, corneal abnormalities (retrocorneal spots varying in size and density and/or an increase in central pachymetry) could be identified on Scheimpflug images before clinical manifestation of the allograft rejection in 9/17 eyes (53%) (Figures 1, 2). In all 9 eyes, retrocorneal spots were observed, and 2 eyes also had a >7% increase in pachymetry. In these 9 eyes, allograft rejection was diagnosed at 22 (±9) months (median: 24 months) after DMEK, although early changes could be detected retrospectively at 8 (±5) months before this time point, at which the eyes were consistently described asymptomatic in slit-lamp examination reports (Figure 2).

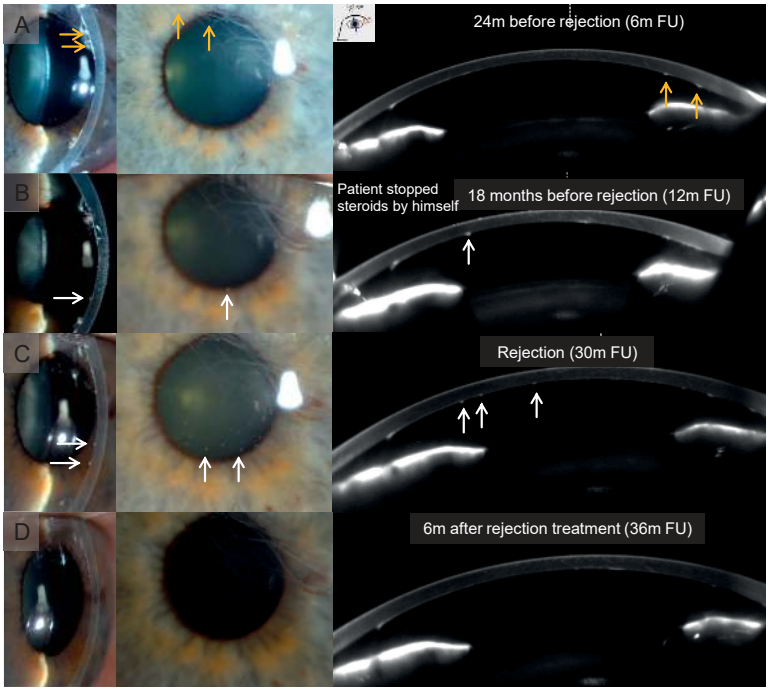

Figure 1. Slit lamp and Scheimpflug images of an eye after Descemet Membrane Endothelial Keratoplasty (DMEK). Images at (A) 6 months, (B) 12 months, (C) 30 months, and (D) 36 months follow-up (FU) after DMEK. Clinical allograft rejection manifested at 30 months postoperatively. In retrospect, keratic precipitates (white arrows) could already be detected 18 months before rejection (B and C) but were not regarded as abnormal during sequential follow-up visits because the eye had a good visual acuity and was completely quiet. Orange arrows outline wrinkles in the graft after partial graft detachment in that area. Six months after treatment (36 months after DMEK), the corneal changes have disappeared (D).

Scheimpflug Images and Pachymetry Findings at the Time of Clinically Manifest Allograft Rejection

When allograft rejection was clinically diagnosed, of the 16 patients (17 eyes), 12 reported either typical subjective complaints (e.g., ocular pain and redness, fluctuating or decreased visual acuity, n = 10) or nonspecific mild ocular discomfort (n = 2), and 4 had no subjective complaints. Objective clinical findings included corneal edema (n = 10) with various degrees of keratic precipitates (n = 17). Except for 2 patients who had discontinued topical steroids on their own initiative, 14 patients still were on a medication regimen of fluorometholone, once every other day and up to 4 times daily, according to the postoperative standard protocol after DMEK.

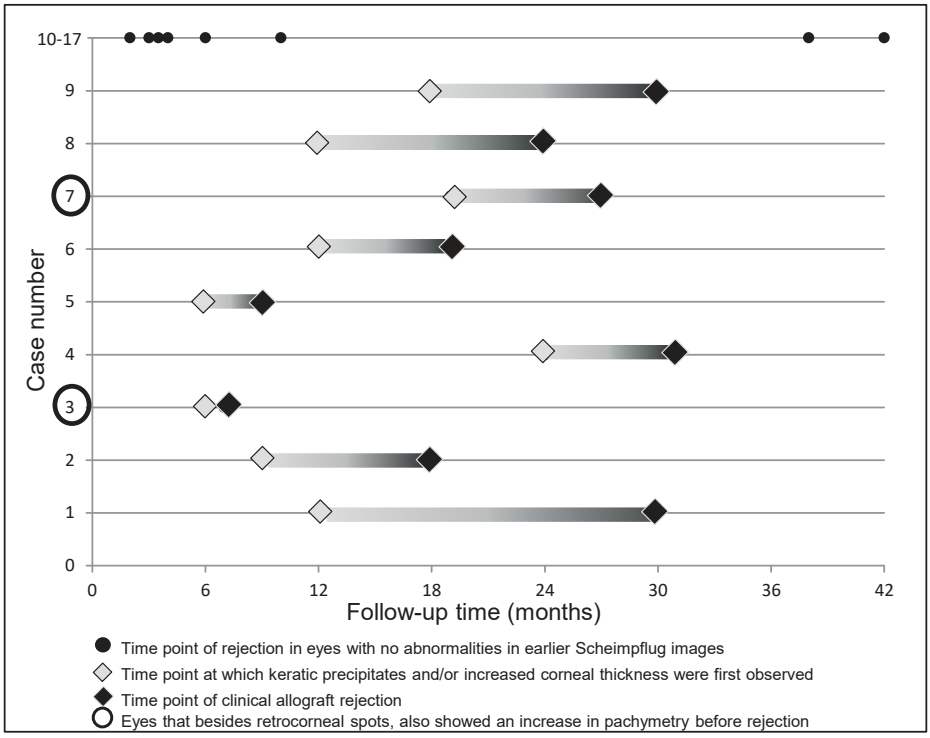

Figure 2. Graph displaying the time points of rejection after Descemet Membrane Endothelial Keratoplasty and the time points of earlier changes as retrospectively detected with Scheimpflug imaging. Time point of rejection (black diamonds) is displayed along with the earlier time points at which in retrospect corneal changes could be found in 9 eyes with Scheimpflug imaging (gray diamonds). Time points of rejection in eyes with no abnormalities in earlier Scheimpflug images (black points) are displayed in the upper line.

At the time of allograft rejection, in 11/17 eyes, Scheimpflug images were made. In 5 of these 11 eyes, the pachymetry differential map showed increased central pachymetry by >7% compared with the previous follow-up point. Furthermore, in 10 of these 11 eyes, retrocorneal (hyper) reflective elevated spots were seen across the endothelium. These spots corresponded to keratic precipitates seen on slit-lamp examination (Figure 1). After intensified topical steroid treatment, pachymetry returned to normal and/or the keratic precipitates disappeared (Figure 1). Four eyes (24%) improved, only for a short time, and later developed graft failure. All eyes had normal intraocular pressure at the time of rejection.

Control Eyes

Throughout the study period, none of the 34 DMEK control eyes matched for patient and donor age (P = 0.86 and P = 0.94, respectively) and baseline charac-

teristics (indication, sex, and lens status) showed any subjective or objective signs indicative of allograft rejection. The average increase in central pachymetry for control eyes ranged from 0.0% to 6.6%, that is, it did not exceed 7% between consecutive postoperative follow-up intervals from 3 to 60 months, and no keratic precipitates were observed.

DISCUSSION

Allograft rejection after DMEK has been reported to occur in 1% to 2% of cases,[10,11] as compared with 5% to 15% in DSEK/DSAEK and PK.[1,3–9] Recently, we reported that endothelial cell changes on specular microscopy may proceed to allograft rejection.[12] To further validate these findings, we commenced the current retrospective study to determine whether changes on Scheimpflug imaging had predictive value for development of allograft rejection.

This study shows that 3 to 6 monthly screening of post-DMEK eyes by Scheimpflug imaging may allow early detection of subtle corneal changes that herald upcoming allograft rejection. In a series of 17 DMEK eyes that developed allograft rejection, more than half of them retrospectively showed corneal changes without subjective symptoms 8 (±5) months before rejection became clinically evident. With Scheimpflug imaging, (hyper)reflective retrocorneal spots corresponding to keratic precipitates varying over time in size and number and/or significant increase in central pachymetry could be found in 9/17 eyes (53%) compared with the previous follow-up examinations. All of these eyes were examined by various ophthalmologists and before allograft rejection became clinically manifest, the relatively subtle changes were not recognized as being abnormal, and no targeted treatment was given.

Postkeratoplasty allograft rejection is typically diagnosed when the patient expresses subjective complaints such as ocular discomfort and/or a drop in visual acuity, which correlate with anterior uveitis and a “red eye.” Compared with PK, “milder” forms of rejection have been described for DSEK/DSAEK and DMEK with patients often lacking subjective complaints as described in about 30% and 80% in DSEK/DSAEK and DMEK, respectively.[6,8,17,18] In our study, about 25% (4/17) of eyes had no subjective complaints, whereas objective clinical signs could be seen on slit-lamp examination.

Our findings concerning the changes in the Scheimpflug imaging before rejection may be surprising for 2 reasons. First, our study may show that more than half of the eyes that were at risk of developing allograft rejection could have been recognized much earlier with Scheimpflug imaging and pachymetry in a "prodromal phase," a phase in which the still (subjectively) asymptomatic eye heralded allograft rejection, months before an immune response became clinically manifest. Second, from the first follow-up point with corneal changes, it took an average of 8 months until rejection manifested. However, rejection is known to be a T-cell–mediated immune response, but the timeline may not agree with the typical time lag (<1 month) for such a reaction to develop full-blown allograft rejection.[19,20]

Early detection of upcoming allograft rejection in eyes that are still asymptomatic may be important to potentially avoid irreversible damage to the graft, because the early keratic precipitates and increased central pachymetry values may be accompanied by significant changes in endothelial cell morphology and a progressive decrease in endothelial cell density.[12,21] Early recognition of these abnormalities could potentially allow for much more effective intervention. That is, in contrast to high-dose steroids after allograft rejection becomes clinically manifest, treatment may now be started long before the damage is done to the endothelium by a massive immune response (Figure 3).

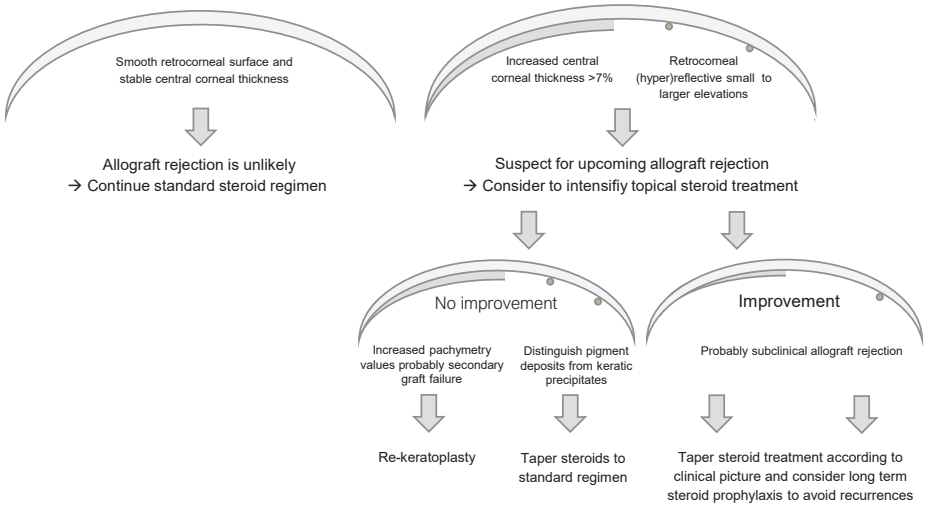

Figure 3. Decision tree for corneal changes (increase in central pachymetry and/or keratic precipitates) preceding allograft rejection, as visualized with Scheimpflug imaging.

There may be 2 reasons why these signs have not been recognized before on slit-lamp examination. First, most eyes that eventually developed full-blown rejection appeared intriguingly "normal" with stable visual acuity, a "white" conjunctiva, a "quiet" anterior chamber, normal pachymetry, and a lack of subjective complaints. Second, against this background, inflammatory deposits were generally overlooked or considered harmless, or misinterpreted as retrocorneal pigment. However, with increasing experience, pigmentary depositions may be better distinguished from keratic precipitates by their finer and crisper appearance, their more abundant location at graft edges, and the fact that they do not change in sequential Scheimpflug images, whereas keratic precipitates would typically increase in number over time, change in size and location, and are often also found centrally. Because the increase in central pachymetry did not exceed 7% in the control eyes, another alarm sign could be a >7% increase in central pachymetry in sequential differential maps.

Furthermore, the time point of the early changes may be of interest, that is, in 9 of the 17 eyes, the immune response may have started at 13 (±6) months (median: 12 months) after surgery, whereas allograft rejection became clinically manifest at 22 (±9) months. This would agree with the observation that most rejections may occur within the first 24 months after keratoplasty.[4,8,22] Thus, Scheimpflug screening may be especially useful within this time frame.

A limitation of our study may be that the predictive value of Scheimpflug imaging in the detection of upcoming allograft rejection would require at least 2 images with a sufficient time interval in between. In our study, 3 eyes showed rejection within the first 3 months, which may not have been detected because the 1-month image did not show a detectable change.

In conclusion, 360-degree Scheimpflug imaging may aid in detecting and documenting minute inflammatory retrocorneal deposits, which may be indicative of upcoming allograft rejection. The possibility to recognize upcoming allograft rejection may benefit treatment in these eyes because it would allow for earlier treatment with steroids to avoid a clinically manifest immune response with substantial endothelial damage. Scheimpflug imaging may have the potential for early detection of eyes that may be at risk to develop allograft rejection. This diagnostic tool could complement specular microscopy for the evaluation of associated corneal endothelial changes.

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