

# Influence of Donor Factors on Descemet Membrane Endothelial Keratoplasty (DMEK) Graft Preparation Outcome

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**Purpose:** To determine which donor characteristics, like previous diseases and surgeries, influence the severity of the DM/endothelial lamella preparation prior to DMEK-surgery.

**Patients and Methods:** Retrospective cross-sectional single-center study is presented. Eight hundred and forty-six eyes with DMEK-surgery between 01/2018 and 01/2021 performed at the University Hospital Cologne, Germany, were included. Information regarding the donors' previous diseases and surgeries were provided by a large database of a cornea bank (Multi Tissue Bank Mecklenburg-Vorpommern) and merged with the Cologne DMEK database, which contains information regarding preparation characteristics of the surgeon-prepared graft directly preoperatively. Three preparation groups (easy, difficult and very difficult) were correlated to the donors' previous diseases and surgeries. The following characteristics were used for the assignment in one of the three groups: stripping difficulty, rolling and staining behavior, central and peripheral adhesences, tissue fragility and DM-splitting.

**Results:** Significant risk factors for DM-splitting were diabetes mellitus (DMel) type II, heart failure, chronic kidney disease and previous cataract surgery ( $p=0.022$ ,  $p=0.012$ ;  $p=0.047$  and  $p<0.001$  respectively). Previous DMel (especially type 2) was significantly associated with the occurrence of central adhesences ( $p=0.009$ ). Several cardiovascular diseases ( $p$ -values between  $<0.001$  and  $p=0.038$ ), DMel type II, chronic kidney disease and previous cataract-surgery were associated with peripheral adhesences ( $p=0.004$ ;  $p=0.020$  and  $p<0.001$  respectively). Furthermore, pseudophakic donor eyes presented a higher degree of fragility of the graft ( $p<0.001$ ). Age was a significant risk factor for difficult preparation ( $p<0.001$ ). The staining of the graft was poorer in donors with chronic kidney disease ( $p=0.037$ ).

**Conclusion:** Donor diabetes mellitus type 2, heart failure, previous cataract surgery, chronic kidney disease and age are associated with a difficult DMEK graft preparation. For every one-year increment in donor age, the odds of having very difficult preparation were increased by 3%. Also, chronic kidney disease predisposes to a poor tissue staining with trypan blue during preparation.

**Keywords:** DMEK, lamellar keratoplasty, donor, graft preparation, risk factors, cornea bank

## Introduction

Descemet membrane endothelial keratoplasty (DMEK) is becoming the gold standard for endothelial keratoplasty worldwide. One key step in performing DMEK is the preparation of the 10 to 15- $\mu$ m-thick Descemet membrane (DM)/endothelial donor lamella. There is mounting evidence that graft preparation properties correlate with donor characteristics. In contrast to penetrating keratoplasty, larger studies analyzing the role of donor factors in DMEK are missing.<sup>1,2</sup>

## Materials and Methods

The COMEDOS study (Cologne Mecklenburg-Vorpommern DMEK Donor Study) analyzes the influence of donor characteristics on graft preparation based on a large data set of donor and recipient information. Out of 1943 consecutive DMEKs performed between 01/2018 and 01/2021 at our department, all records on grafts that came from the Mecklenburg-Vorpommern cornea bank (n=846), including donor information, were included. DMEK surgeries were performed by three surgeons (BB, CC and MM) in a standardized way.<sup>3,4</sup>

The DMEK lamella was stripped directly preoperatively by the surgeon. Afterwards, the surgeon completed a questionnaire and classified the difficulty of the lamella preparation and tissue preparation behavior using a standardized form. This included details regarding stripping difficulty, rolling and staining behavior, central and peripheral adherences, tissue fragility and DM-splitting. In addition, four criteria were used to define the difficulty of graft preparation: 1) existence of central DM attachments, 2) existence of peripheral DM attachments, 3) occurrence of DM-splitting and 4) fragility of the DM complex. The tissue was regarded as fragile if the tissue fell apart when gently pulled at by a forceps. Based on these four criteria, three groups were formed: 1. easy preparation – if all four criteria were negative, 2. difficult preparation – if one criterion was answered with “yes” and 3. very difficult preparation – if two or more criteria were answered with “yes”.

Demographic and medical data of all donors were retrieved from the Mecklenburg-Vorpommern cornea bank database (including age, preexisting ophthalmological and general diseases, nicotine) and merged with the prospectively collected data of the recipients from the Cologne DMEK database, using the RED-Cap (Research Electronic Data Capture) electronic data capture tool.<sup>5</sup>

Data were analyzed in SPSS (version 29.0; SPSS, Inc, Chicago, IL) using Wilcoxon signed exact test, Pearson's Chi-square test and univariable odds ratio analysis. The multivariable analysis was adjusted with multicollinearity (variance inflation factor >10). The level of significance was set at 0.05.

## Results

The analysis contains data from 707 donors and 846 recipients. Regarding donor diagnosis, complete data from 699 out of 846 eyes were available. One hundred and thirty-nine donors donated both eyes.

From the donor population, 55.6% were male and the median age was 80 years (range 37–93 years). From transplant recipients, 53.1% were female (n=845; one missing value) and the median age was 69 years. 46.3% of the donor eyes had a previous cataract surgery.

The top 10 medical diagnoses of the donors were (descending order): arterial hypertension, diabetes mellitus (DMel) type II, chronic renal failure, atrial fibrillation, chronic ischemic heart disease, heart failure, hypercholesterolemia, hyperkalemia, atherosclerosis and respiratory insufficiency.

When analyzing donor factors for their relevance on DMEK preparation behavior and outcome, several risk factors were identified (see Table 1).

Significant risk factors for DM-splitting were DMel type II, heart failure, chronic kidney disease and previous cataract surgery. In a multivariable model, heart failure and preexisting diabetes together increased the risk of the graft of having DM splitting by 2.87-fold.

A total of 106 eyes had central adherences. Out of these, 86.8% (n=92) grafts were used and 13.2% (n=14) were discarded. In this subanalysis regarding only the eyes with central adherences, DMel type II (n=699, OR 1.75; 95% CI 1.15–2.67, p=0.009) and previous diabetes history (n=692, OR 2.02; 95% CI 1.01–3.11, p=0.002) were associated risk factors. Previous diabetes history refers to history of diabetes mellitus regardless of type or severity.

Essential hypertension (OR=1.56, 95% CI 1.08–2.26, p=0.019), DMel type II (OR=1.55, 95% CI 1.15–2.08, p=0.004), chronic kidney disease (OR=1.43, 95% CI 1.06–1.93, p=0.020), atrial fibrillation and atrial flutter (OR=1.73, 95% CI 1.28–2.34, p<0.001), heart failure (OR=1.66, 95% CI 1.22–2.25, p=0.001), atherosclerosis (OR=1.44, 95% CI 1.02–2.02, p=0.038) and previous cataract surgery (OR=24.06, 95% CI 16.18–35.76, p<0.001), were found to be significant risk factors for peripheral adherence (n=696, see Table 1).

Only previous cataract surgery was found as a significant risk factor for the fragility of the tissue (see Table 1).

**Table I** Synopsis of Donor Factors and Their Impact on Each Preparation Characteristics of the Descemet Membrane-Endothelial Complex During Graft Preparation for DMEK Surgery. Age and a Previous Cataract Surgery Were Related to a Difficult or Very Difficult Preparation

Preparation Characteristics	Donor Characteristics	n	OR	95% CI	P value
DM splitting	DMel type II	699	1.47	1.06–2.05	0.022
	Heart failure	699	1.53	1.10–2.13	0.012
	Previous diabetes*	692	1.49	1.07–2.07	0.020
	Previous cataract surgery	699	3.09	2.18–4.38	<0.001
	Chronic kidney disease	699	1.39	1.01–1.94	0.047
Central adherence	DMel type II	699	1.75	1.15–2.67	0.009
	Previous diabetes*	692	2.02	1.01–3.11	0.002
Peripheral adherence	Essential hypertension	696	1.56	1.08–2.26	0.019
	DMel type II	696	1.55	1.15–2.08	0.004
	Chronic kidney disease	696	1.43	1.06–1.93	0.020
	Atrial fibrillation and atrial flutter	696	1.73	1.28–2.34	<0.001
	Heart failure	696	1.66	1.22–2.25	0.001
	Atherosclerosis	696	1.44	1.02–2.02	0.038
	Previous cataract surgery	696	24.06	16.18–35.76	<0.001
Fragility of tissue	Previous cataract surgery	697	1.79	1.27–2.51	<0.001
Preparation groups	Previous cataract surgery	699	1.97	1.65–2.29	<0.001

**Note:** \*Previous DM: means history of diabetes mellitus regardless of type or severity.

**Abbreviations:** DM, Descemet membrane; DMel, diabetes mellitus.

Additionally, chronic kidney disease predisposed to a poor staining of the graft with trypan blue (coeff  $-0.4154$ ,  $p=0.037$ ).

We found previous cataract surgery to be significantly associated with stripping difficulty and preparation group (difficult and very difficult group; all Chi-sq  $p<0.001$ ). The estimated positive significant effects showed that previous cataract surgery increased the difficulty of stripping by 0.96 fold (95% CI 0.66–1.25) and the overall difficulty of the preparation by 1.97 fold (95% CI 1.65–2.29).

In addition, the donor age distribution ( $p<0.001$ ) and median ages ( $p=0.002$ ) across the preparation groups were significantly different. Age was a significant risk factor for the preparation group ( $p<0.001$ ) and older patients related to a very difficult preparation. For every one-year increment in age, the odds of having very difficult preparation were increased by 3% (OR=1.03 95% CI 1.01–1.04).

From the available nicotine consumption status of 23% of donor eyes, 86.8% used to smoke, but no association of preparation behavior with donors' nicotine consumption was found ( $p=0.212$ ).

When analyzing the association of the donor diagnosis to the three preparation group classifications (easy, difficult and very difficult), DMel II and heart failure were identified as having a significant association ( $p=0.003$  and  $p=0.036$ , respectively).

## Discussion

In this preliminary analysis, we determined several donor factors associated with a difficult preparation of the Descemet membrane (DM)-endothelial graft complex for DMEK surgery. One of the risk factors is diabetes mellitus type II.

Published data suggest that preparation of the DM graft is influenced by donor diabetes mellitus.<sup>6</sup> We confirm this and in addition found several novel donor-related risk factors complicating DM preparation such as age, previous cataract surgery, heart failure and chronic kidney disease.

Regarding the role of donor age as a risk factor for difficult preparation, there are only few studies yet that analyzed the influence of donor age on graft preparation for DMEK surgery.<sup>7–9</sup> Most of the studies refer to associations between donor age and postoperative outcome parameters.<sup>10,11</sup> Bennett et al determined the scroll width of the DM-endothelial complexes and associated this with donor age, showing that graft from older donors showed a reduced scroll tightness after preparation. However, this analysis was performed in 26 corneal scleral buttons from donors with a mean age of  $59 \pm 17$  and a range of 15–69 years.<sup>7</sup> Steven et al showed in 26 eyes by means of intraoperative optical coherence tomography (OCT), that DM rolling behavior showed significant inverse correlation between donor age (range, 39–93 years) and the extent of rolling  $R^2 = 0.5$  ( $p=0.006$ ).<sup>8</sup> Heinzelmann et al also showed in a small cohort of 28 grafts, that the older the donor (mean age  $74.8 \pm 12.6$  years) the broader were the rolls DM spontaneously forming when it was placed into buffered saline solution.<sup>9</sup> In our cohort, the mean age was 80 years (range 37–93 years;  $n=846$  eyes). We determined in our cohort, that for every one-year increment in age, the odds of having very difficult preparation increased by 3%, suggesting that grafts from older donors lead to a more difficult preparation. From a clinical point of view, it is known that with increasing age, the thickness of the DM increases by deposition of collagen and extracellular matrix components.<sup>12</sup> This may lead to a more difficult separation of the layers during preparation with increasing age of the donor. Also, the fragility of the tissue increases and with age more patients have undergone cataract surgeries or other corneal surgeries leading to focal sites of pathological adherence. In a future study, we will determine in detail the impact of donor age on the postoperative clinical outcome after DMEK.

Previous studies analyzed the role of pseudophakic donors on the postoperative endothelial cell density showing that the endothelial cell loss and graft survival rates are comparable to those grafts from phakic donors.<sup>13,14</sup> Our study determines, for the first time, the influence of previous cataract surgery on graft preparation and demonstrated that the preparation of grafts from pseudophakic donors represents a risk factor for a more difficult preparation.

Heart failure and chronic kidney disease are novel risk factors and their role will also need to be further examined.

## Conclusion

Donor comorbidities play an important role in structural changes of the corneal architecture and thus in the preparation behavior of the inner layers of a donor cornea for DMEK surgery.<sup>6</sup> The most important comorbidities that negatively influence the graft preparation of a surgeon-prepared DMEK graft are diabetes mellitus type II, previous cataract surgery, heart failure and chronic kidney disease. Furthermore, for every one-year increment in donor age, the odds of encountering a very difficult preparation were increased by 3%. This should be taken into account when selecting and preparing donor tissue for DMEK surgery either by the surgeon or a cornea bank.

## Meeting Presentation

ARVO 2023 New Orleans, La, USA (poster presentation).

## Ethics Statement

The study was conducted in adherence to the tenets of the Declaration of Helsinki and was approved by the local Institutional Review Board (Ethics Commission of Cologne University's Faculty of Medicine, Cologne, Germany; No. 14-373). All patients gave their informed consent.

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## Disclosure

Professor Björn Bachmann reports personal fees from Heidelberg Engineering, outside the submitted work; In addition, Professor Björn Bachmann has a patent DMEK shooter system issued (EP3474776 B1, US 10,874,504, PCT/EP2020/055687, PCT/EP2020/072701). The authors report no other conflicts of interest in this work.

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