# Implementation of a Diabetes Rating Scale Can Reduce DMEK Graft Preparation Failure Among Less Experienced Technicians

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## ABSTRACT

**Purpose:** To compare rates of graft preparation failure (GPF) during Descemet membrane endothelial keratoplasty (DMEK) processing before and after implementing a previously published rating scale. Donor tissues rated 1-3 had mild diabetes and low risk of GPF; those rated 4-5 had severe diabetes and high risk of GPF.

**Methods:** Retrospective review of donor corneas for DMEK processing from 2012-2020 at a single eye bank with post hoc analysis.

**Results:** Of 3,376 donor corneas processed for DMEK following diabetes scale implementation, 24.6% had diabetes. Grafts rated 4-5 with rating known to the technician (i.e. after scale implementation) (n=314) had a GPF rate of 5.4%. Post-hoc analysis of tissues with the same rating but unknown to the technician (n=60) had a GPF rate of 25.0% (P<0.01). For grafts rated 1-3, the GPF rate was 4.6% vs. 3.3% before and after implementation of the scale, respectively (P=0.48). For experienced technicians (>150 tissues processed), no significant difference was seen in GPF rates for diabetic tissue following implementation of the diabetes rating scale (4.6% vs. 3.7%, p=0.70). For inexperienced technicians, however, the GPF rate fell significantly after the scale (15.0% vs. 6.3%, p=0.02).

**Conclusions:** Knowledge of diabetic status and severity prior to processing can help eye bank

technicians, particularly those with limited experience, mitigate risk of GPF.


Descemet membrane endothelial keratoplasty (DMEK) is a procedure performed on patients with endothelial disease of the cornea that involves selective transplantation of Descemet membrane. Compared to alternative approaches such as Descemet stripping endothelial keratoplasty (DSEK), DMEK may have lower rejection rates (Anshu et al. 2012; Ang et al. 2016; Woo et al. 2019)Descemet's stripping endothelial keratoplasty (DSEK and may result in better visual acuity (Price et al. 2009; Tourtas et al. 2012). The number of DMEK procedures performed in the United States has increased every year since 2012, with over 13,000 procedures performed in 2019 (Eye Bank Association of America 2020). Increased DMEK demand has led to concern over whether the supply of tissue from eye banks can meet demand (Ostrander et al. 2019)congenital hereditary endothelial dystrophy, bullous keratopathy, and iridocorneal endothelial (ICE.

Multiple factors, including technician experience (Vianna et al. 2015; Parekh et al. 2018) and donor diabetic status (Greiner et al. 2014; Price et al. 2017), can affect DMEK processing outcome. Diabetic tissues are more likely to fail during processing with graft preparation failure (GPF) rates ranging from 5-16% compared to 1-2% in non-diabetic tissue (Greiner et al. 2014; Vianna et al. 2015; Price et al. 2017). The severity of diabetes, using markers such as duration of diagnosis or presence of co-morbidities (e.g.

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**Code availability**: Stata code in data analysis is available from the authors upon request.

**Ethics Approval**: The Legacy Research Institute IRB reviewed and approved the use of Lions VisionGift eye bank database for studies in which no patient identifying information is accessed.


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hyperlipidemia or obesity), is also positively correlated with increased GPF rates (Vianna et al. 2015). One hypothesis for the increased GPF rate is abnormal adhesion between the interfacial matrix and posterior stroma in diabetic tissue (Schwarz et al. 2016)we established an experimental technique for quantifying the force required to separate the endothelium-Descemet membrane complex (EDM.

A previous study developed a 5-point diabetes rating scale to quantify the effect of diabetes on GPF (Williams et al. 2016). One point was assigned for each of the following: a history of diabetes, body mass index > 30kg/m$^2$, or hypertension. Two points were assigned for any of the following: diabetes history ≥ 10 years, type 2 diabetes with outpatient insulin dependence, or diabetic comorbidities, including diabetic neuropathy, nephropathy, or retinopathy, peripheral vascular disease, or a diabetes-related amputation. After retrospectively assigning scores to diabetic tissue, the authors determined that tissues with severe diabetes (DM 4-5), but not mild diabetes (DM 1-3), had an increased risk of GPF. Implementation of this scale at Lions VisionGift (Portland, OR) resulted in the diversion of severely diabetic tissue away from DMEK processing to other transplant types. Of equal importance, the scale resulted in technicians' systematized awareness of not only whether the tissue being peeled for DMEK was affected by diabetes, but also *the severity* of diabetes, which previously had not been part of the donor history.

It remains unknown whether prior knowledge of donor diabetes severity affects GPF rates. Our study aims to determine if incorporation of this diabetes rating scale and prior technician knowledge of donor diabetes severity affected DMEK processing outcomes. Furthermore, we assessed the impact of technician experience in the context of processing diabetic tissue.

## METHODS

### Study Population

Data on DMEK processing at Lions VisionGift from 2012-2020 were retrieved using the eye bank's database management system. The Legacy Research Institute IRB reviewed and approved the use of Lions VisionGift eye bank database for studies in which no patient identifying information is accessed, as is the case in this study. All non-imported grafts with intent for DMEK transplant were included. This data was used to compare GPF rates in diabetic tissue before and after the implementation of the diabetes rating scale.

### Rating Scale

A 5-point diabetes rating scale outlined by Williams et. al (2016), classified the severity of diabetes in donors. Based on this study, tissues rated DM 1-3 were sub-classified as mild diabetes with few or no co-morbidities while those rated DM 4-5 were sub-classified as severe diabetes with associated co-morbidities.

### Post-hoc Analysis

The post-hoc analysis compared DMEK processing outcomes for donors with a diabetes rating between the current study and that of Williams et. al (2016) as a control group (N=125). Only tissues processed after the implementation of the diabetes rating scale in March 2015 were included (i.e. with the tissue's diabetes rating provided to technicians).

### Outcome Measures

The primary outcome measure was DMEK GPF, defined as tissue that could not be transplanted due to damage incurred during processing. Examples of possible GPFs include a tear within the central clear zone of endothelium or >20% endothelial cell loss during post-processing evaluation via slit lamp and specular microscopy. Consistent with prior studies (Vianna et al. 2015; Parekh et al. 2018), we defined a technician as experienced (i.e. past the DMEK learning curve) after processing 150 DMEK tissues.

### Statistical Analysis

Descriptive statistics were performed on donor demographic information and tissue processing metrics (e.g. donor age, endothelial cell density, death-to-processing time, median processing time, and subjective tissue peel difficulty). Median processing times for non-diabetic tissues, DM 1-3, and DM 4-5 tissue were calculated for pre-stripped, pre-loaded tissues and compared using a Mann Whitney test. GPF before and after the implementation of the diabetes rating scale was compared using a post-hoc Pearson's chi-squared test and Fisher's exact test. Multivariate logistic regression was used to determine odds of GPF by diabetes severity after controlling for donor age, death-to-preservation time, pre-processing endothelial cell density, and technician experience (defined as a technician having processed 150 DMEK tissues or not). GPF rates stratified by technician experience were calculated using a Pearson's chi-squared test. A $P$-value <0.05 was considered statistically significant. All analyses were performed using Microsoft Excel 2018 (Microsoft Corp., Redmond, Washington) and StataCorp version 16 (StataCorp LP, College Station, Texas, USA).


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## RESULTS

Following the implementation of the diabetes rating scale in March 2015, 24.6% of 3,376 donor corneas processed for DMEK had diabetes. While average age was significantly higher in both DM 1-3 and DM 4-5 groups compared to non-diabetic donors, only DM 4-5 had an endothelial cell density (ECD) significantly different from the non-diabetic group. No significant differences were seen in the death to preservation (D-P) time points or median processing times when comparing non-diabetic tissue, DM 1-3 tissue, or DM 4-5 tissue (Table 1).

***Table 1:*** *Selected tissue characteristics by diabetes rating scale category following implementation of the diabetes rating scale (N=3,376*

| Characteristic | Non-diabetic | DM 1-3 | DM 4-5 |
|---|---|---|---|
| Average age (SD) | 64.8 (7.9) | **66.4 (7.3)** | **66.3 (7.3)*** |
| ECD (SD) | 2732 (300) | 2755 (312) | **2784 (322)*** |
| D-P (hours) (SD) | 10.7 (4.5) | 10.9 (4.3) | 10.53 (4.1) |
| Median Processing Time (min) | 25 | 25 | 26 |

*Bolded values indicate a significant difference (P<0.05) compared to non-diabetic tissue

ECD: endothelial cell density prior to processing; D-P: death to preservation time

Seventeen tissues (3.3%) rated DM 1-3 and 17 tissues (5.4%) rated DM 4-5 experienced GPF following implementation of the diabetes rating scale when technicians were prospectively made aware of donor diabetic status (Table 2). When comparing DM 4-5 rated tissue in our study to that previously published by Williams et al. (2016), tissues experienced GPF at a significantly lower rate after implementation of the diabetes rating scale compared to before (5.4% vs. 25.0%, P<0.01). No significant difference was seen for tissues rated DM 1-3 in this same analysis (3.3% vs 4.6%, P=0.48). Non-diabetic tissues had a GPF rate of 1.7%, compared to 4.1% for diabetic tissues.

***Table 2:*** *Post-hoc analysis comparing DMEK tissue preparation outcomes by diabetes rating after the implementation of the diabetes rating scale to Williams et al. (2016)*

| Processing Outcome | Williams et al. (2016) | Current Study | *P* |
|---|---|---|---|
| DM 1-3 Failure (%, N) | 4.6 (3/65) | 3.3 (17/519) | 0.48 |
| DM 4-5 Failure (%, N) | 25.0 (15/60) | 5.4 (17/314) | **<0.01** |
| Non-diabetic Failure (%, N) | - | 1.7 (44/2543) | - |
| Diabetic Failure (%, N) | 14.4 (18/125) | 4.1 (34/833) | - |

After controlling for donor age, death-to-preservation time, pre-processing endothelial cell density, and processor experience, a DM 1-3 rating on the diabetes scale conferred an odds ratio (OR) of 1.84 (P=0.04) for GPF compared to non-diabetic tissue while the OR increased to 3.28 for tissues rated DM 4-5 (P<0.01) (Table 3). An increased OR of 1.78 was found for GPF for DM 4-5 tissue compared to DM 1-3 tissue, however this finding was not statistically significant (P=0.10).

***Table 3:*** *Multivariate logistic regression comparing odds of failure by diabetes rating among tissues processed after implementation of the diabetes rating scale controlling for donor age, death-to-preservation time, pre-processing endothelial cell density, and processor experience.)*

| | OR | *P* | SE | 95% CI | N |
|---|---|---|---|---|---|
| Non-diabetic vs DM 1-3 | 1.84 | **0.04** | 0.54 | 1.04-3.26 | 3062 |
| Non-diabetic vs DM 4-5 | 3.28 | **<0.01** | 0.97 | 1.84-5.84 | 2857 |
| DM 1-3 vs DM 4-5 | 1.78 | 0.10 | 0.63 | 0.88-3.55 | 833 |

From 2012-2020, our dataset included a total of nine DMEK processing technicians. For non-diabetic tissue, inexperienced technicians (≤150 tissues processed) had a GPF rate of 6.5% during the learning curve phase compared to 2.7% after becoming experienced (>150 tissues processed) (P<0.001) (Supplemental Table 1). For diabetic tissue, inexperienced technicians had a GPF rate of 10.3%

***Supplemental Table 1:*** *DMEK processing failure rate for diabetic and non-diabetic tissue for inexperienced (<150 tissues processed) and experienced (>150 tissues processed) technicians from 2012-2020.*

| | Inexperienced | Experienced | *P* |
|---|---|---|---|
| Non-diabetic tissue (%, N) | 6.5% (67/1026) | 2.7% (90/3346) | **<0.001** |
| Diabetic tissue (%, N) | 10.3% (27/263) | 3.7% (29/776) | **<0.001** |

during the learning curve phase and 3.7% after becoming experienced (P<0.001). We next examined GPF rates in inexperienced and experienced technicians before and after technicians were notified of donor diabetes status. The GPF rate fell significantly for inexperienced technicians after being notified of donor diabetes status (15.0% vs. 6.3%, P=0.02), but not for experienced technicians (4.6% vs. 3.7%, P=0.70) (Table 4).

***Table 4:*** *DMEK processing failure rate in diabetic tissue for inexperienced (<150 tissues processed) and experienced (>150 tissues processed) technicians prior to and after the implementation of the diabetes rating scale from 2012-2020.*

| | Prior to scale | After scale | *P* |
|---|---|---|---|
| Inexperienced (%, N) | 15.0% (18/120) | 6.3% (9/143) | **0.02** |
| Experienced (%, N) | 4.6% (3/65) | 3.7% (26/711) | 0.70 |


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## DISCUSSION

Consistent with previous reports (Greiner et al. 2014; Vianna et al. 2015; Price et al. 2017), we find that diabetes remains a major risk factor for DMEK GPF. In addition, we find that diabetes severity positively correlates with GPF rate. Williams et al. (2016) retroactively assigned diabetes ratings to donor DMEK tissue and found that tissue from severely diabetic donors (i.e. tissue rated DM 4-5) had a GPF rate of 25% compared to 4.6% in less severe diabetic tissue (DM 1-3). In this study, we report that prospectively rated DM 4-5 tissue had a significantly lower GPF rate of 5.4%. DM 1-3 tissue also had a decreased GPF rate of 3.3%, but this difference failed to reach statistical significance. The overall processing GPF rate for diabetic tissues after the implementation of the rating scale was 4.1% in our study, a rate lower than the 5-16% rate previously reported for diabetic tissue (Greiner et al. 2014; Vianna et al. 2015; Price et al. 2017). While previous studies have provided potential explanations for the inherent difficulties in utilizing diabetic tissue for DMEK processing (Schlötzer-Schrehardt et al. 2013; Schwarz et al. 2016), our study suggests that technician experience and knowledge of diabetes status can modify DMEK processing outcomes. One reason for improved outcomes could be from conscious or subconscious changes in technicians' approach to processing diabetic tissue, which is known to be more likely to tear.

In contrast to Williams et al, we find that DM 1-3 tissues have a significantly increased rate of GPF compared to non-diabetic tissue. Differences between our results for DM 1-3 tissue could be due to the smaller sample size in the previous study, which included 65 DM 1-3 tissues compared to 519 DM 1-3 tissues in our dataset. These results suggest that eye banks should consider prioritizing non-diabetic tissue for DMEK processing before mildly diabetic tissue or severely diabetic tissue.

There is a known steep learning curve for DMEK (Vianna et al. 2015; Parekh et al. 2018). In our study, technicians were defined as experienced after processing 150 DMEK tissues. Diabetic tissue processed by inexperienced technicians had the highest rate of DMEK GPF. Therefore, assigning diabetic tissue, particularly severely diabetic tissue, first to experienced technicians may improve yield for eye banks. Such an allocation may be advantageous because some eye banks (including Lions VisionGift) currently have protocols that re-allocate tissue away from the DMEK pool should a mate tissue experience GPF (Stoeger et al. 2017). This is because mated tissues are more likely to experience GPF if the first tissue in a mated pair fails (Gorovoy et al. 2014). As a result, diabetic tissues that fail in the hands of inexperienced technicians could incur collateral DMEK tissue loss. If inexperienced technicians must process diabetic tissue, eye banks may consider using a diabetes rating scale as a tool to reduce tissue loss, given the improvement in tissue processing seen in this group with the scale.

Currently, potential DMEK donor tissue undergoes an extensive screening process to screen out tissues with extensive cataract scars, young donor age, and low endothelial cell density (Heinzelmann et al. 2014; Holiman et al. 2015). The identification of diabetes as a risk factor for GPF has raised the question of whether to exclude or limit diabetic tissue from the donor pool (Greiner et al. 2014; Vianna et al. 2015). However, diabetes is common in the general population and exclusion of diabetic donors could remove up to one-third of the potential DMEK donor pool (Greiner et al. 2014; Price et al. 2017). Furthermore, the prevalence of diabetes among adults in the United States is expected to increase from 10.8% in 2019 to 12.1% by 2030 (International Diabetes Federation 2019).

For many eye banks, the demand for DMEK has necessitated the use of diabetic tissue. Paired with the recent impact of the coronavirus pandemic on DMEK tissue supply (Busin et al. 2020), it is likely that diabetic tissue will continue to play a large role in the potential DMEK donor pool. Although diabetic tissue is more difficult to prepare, it has not been shown to impact air reinjection, endothelial cell loss, or graft survival (Price et al. 2017). Thus, factors that reduce DMEK GPF in diabetic tissue may improve the supply of donor DMEK tissue without compromising outcomes.

There are several limitations to this study. First, technicians vary in experience and GPF rates. Those with high GPF rates may leave the eye bank or transfer roles, biasing the rate. In addition, Williams et. al (2016) had a small sample size of 125 grafts, so the reported rate of GPF of 25% for severely diabetic tissue may be skewed, thus affecting the post-hoc analysis. Finally, following implementation of the diabetes rating scale, the tissue processing protocol at this eye bank was modified to exclude tissue mates of diabetic tissue with a high rating that experienced GPF, which may artificially decrease the GPF rate (Stoeger et al. 2017).

In this study, we examined the impact of a diabetes rating scale on DMEK GPF rates. This scale, which prospectively rates diabetic severity of a tissue, resulted in a significantly decreased GPF for diabetic tissue. The effect was especially notable for inexperienced technicians. In addition to notifying technicians of donor diabetic status, assigning diabetic tissue to experienced technicians, and prioritizing allocation of tissues according to diabetes severity can increase the supply of DMEK tissue.


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