# Descemet Membrane Endothelial Keratoplasty (DMEK) Tissue Preparation: A Donor Diabetes Mellitus Categorical Risk Stratification Scale for Assessing Tissue Suitability and Reducing Tissue Loss

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**Purpose:** This study assessed a novel diabetes mellitus (DM) rating scale in relation to its utility in reducing Descemet membrane endothelial keratoplasty (DMEK) tissue preparation failure.

**Methods:** A 5-point DM rating scale was defined, in which 1 demonstrated relatively good health associated with DM and 5 represented comorbidities associated with DM. A chart review from consecutive donors who had at least 1 tissue prepared for DMEK was performed. Using the donor profile, the first tissue processed from each donor was categorized according to the DM severity and if the tissue passed or failed the DMEK preparation. Failure rates per rating group were evaluated using logistic regression and odds of preparation failure.

**Results:** A total of 125 tissues prepared for DMEK were categorized based on the defined DM rating scale. Of these, 9 tissues were rated 1 (11.1% failure), 25 were rated 2 (0% failure), 31 were rated 3 (6.5% failure), 24 were rated 4 (16.7% failure), and 36 were rated 5 (30.6% failure). The odds ratios were significant for tissues rated as 5 and 3 ($P < 0.05$). No other rating categories were found to influence the odds of failure. A $\chi^2$ test comparing categories of low risk (1–3) and high risk (4–5) was also performed ($P = 0.001$).

**Conclusions:** The DM rating scale does seem to stratify the risk of preparation failure associated with the severity of DM and associated comorbidities. Inclusion of some diabetic donors for the preparation of DMEK grafts may be warranted given proper screening of the donor history and application of the rating scale.

**Key Words:** DMEK, cornea preparation, eye bank, diabetes mellitus, cornea processing

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The corneal endothelial monolayer is responsible for the "pump/leak" functionality that maintains corneal clarity. Dysfunction in this layer of cells allows fluid buildup in the stroma and ultimately the loss of visual clarity. Currently, the loss or dysfunction of these cells requires transplantation of donor cells to restore function to this layer and ultimately restore and retain vision. Great advances have been made in the replacement of these cells with the advent of endothelial keratoplasty. Endothelial keratoplasty itself has evolved greatly over the past 15 years.[1] There is still some debate about the ideal surgical replacement for the endothelium, but what is not debatable is that Descemet membrane endothelial keratoplasty (DMEK) is becoming increasingly more popular with surgeons, and eye banks are quickly adopting in-house processing programs for the preparation of these grafts.[2]

A number of excellent articles have been published to assist the surgeon or eye bank technician with the initial part of DMEK surgery, that of tissue preparation.[3–7] Although the literature gives guidance for tissue preparation, no technique is foolproof and tissue wastage remains a serious concern for eye banker and surgeon alike. Additional technique papers have been published to give guidance to issues that arise during the tissue preparation.[8,9] Although these techniques demonstrate good results in expert hands, there is not uniform success. Questions remain about why one membrane would be easier to prepare than another and why difficulty in peeling so often comes in pairs from the same donor.[8,9] It has been proposed that the structure of the individual membrane itself is to blame in at least some cases for the difficult graft peeling, or "stickiness," that plagues some membrane preparations and is seemingly absent from others.[10]

Although the knowledge that the structure may be to blame for some graft preparation failures may give us some solace, it does little to protect the tissue supply or prevent preparation failures if these tissues cannot be identified in advance. To that end, a study by Greiner et al[11] proposed a relationship between diabetes mellitus (DM) and the "stickiness" encountered in difficult-to-prepare DMEK grafts. It was found that the exclusion of diabetic donors produced a failure rate of 1.9% versus the failure rate of 15.3% in the diabetic donor pool. Thus, the exclusion of diabetic donors for DMEK significantly reduces the tissue loss associated

with preparation. With DMEK tissues in limited demand in the United States in 2013,[2] it was better to exclude these tissues altogether rather than risk ruining a graft with a healthy endothelium that could just as easily be used for Descemet stripping automated endothelial keratoplasty (DSAEK) or penetrating keratoplasty. Vianna et al[12] further refined our understanding of the risks associated with preparation failure by including hypertension (HTN), hypercholesterolemia, obesity, and DM duration in the list of factors to consider when selecting donor tissue with the least likelihood of failure.

As DMEK grows in popularity, finding a suitable number of donor tissues with a low risk for preparation failure becomes increasingly important. Cataract surgery scars may limit the graft size, endothelial cell counts must be sufficient to meet more selective surgeons' parameters, and older donors are preferred to have a thicker and easier-to-handle DMEK graft that does not scroll too tightly in the anterior chamber.[9,13,14] With all these factors in play, the exclusion of diabetic donors can stress the DMEK donor pool. With this in mind, Lions VisionGift (Portland, OR) created a DM rating scale informed by the articles by Vianna et al[12] and Greiner et al[11] with the goal of including some diabetic donors without increasing the risk of donor tissue preparation failure. In this article, we define a 5-point rating scale and assess its utility in excluding inappropriate donors. For testing practical implementation of the scale, we predicted that categories 1 to 3 will have lower occurrences of preparation failure as a group when compared with categories 4 and 5 as a group.

## METHODS

This was a retrospective study using an institutional review board–monitored, Health Insurance Portability and Accountability Act–compliant, electronic eye bank database. This research adhered to the tenets of the Declaration of Helsinki. Between September 2012 and February 2015 all donors with a history of DM and at least 1 tissue prepared for DMEK with the intent to transplant were identified. All tissues were prepared at one location (Lions VisionGift) by trained processing technicians.

### Rating Scale

The severity of the donor's DM was categorized with a simple 5-point rating scale. A score of 1 indicated the presence of DM but relatively good health and lack of DM-related complications. A score of 5 indicated the presence of DM accompanied by poor health and associated complications of DM. This scale uses readily available donor medical history and DM status recorded at the time of tissue donation. Prior publications[11,12] informed the rationale for selection of factors deemed relevant to increased failure rates in DMEK preparation. The characteristics identified were HTN, obesity (body mass index $>$ 30), DM duration greater than 10 years, as well as secondary comorbidities such as neuropathy, nephropathy, or retinopathy demonstrative of end-organ damage secondary to DM. Each donor was evaluated for these attributes and given a numerical rating. To be given a rating, the donor must have a current diagnosis of DM reported in the donor record. If the donor had a diagnosis of DM without any other characteristics listed above, a base rating of 1 was given. Another single point was assigned for body mass index $>$30, and another point for the presence of HTN. Two points were given if any one of the following were found in the donor's medical profile: DM lasting at least 10 years, evidence of DM requiring insulin (out of hospital), or a secondary comorbidity that could be attributed to DM, such as the ones previously listed. The rating scale is summarized in Table 1.

### Application of the Rating Scale/ Donor Characteristics

All diabetic donor corneas processed for DMEK were retrospectively identified, and the donor records were reviewed by a single researcher (R.S.W.) with extensive experience in donor record reviews. If both the right and left tissues were processed, we chose to only include the first tissue processed in this analysis. In total, 125 consecutive donors with at least 1 corneal tissue processed for DMEK between September 2012 and February 2015 were reviewed.

Using the donor medical profile, processed tissue was categorized with our novel 5-point rating scale. Once the tissue was categorized with the DM rating scale, it was subcategorized into 2 groups; if the tissue was successfully peeled for DMEK, it was assigned to the "pass" group and if the tissue tore and was unable to be used for surgery, it was assigned to the "fail" group.

### Statistical Analysis

Statistical analyses were performed with commercially available software packages (SPSS version 23; SPSS, Inc, Chicago, IL; Excel 2013; Microsoft Corporation, Redmond, WA). Logistical regression analysis was performed to assess the 5 risk categories for statistically significant increases or decreases in the odds of tissue preparation failure. Additionally, we used 1-way analysis of variance tests with a posthoc

**TABLE 1.** Diabetes Risk Categorization Tool

| Found in Donor History | Point Value Assigned |
|---|---|
| Any history of DM | 1 |
| Body mass index $>$30 kg/m$^2$ | 1 |
| HTN | 1 |
| Any one of the following: | 2 |
| DM history lasting at least 10 yrs, DM type 2 with outpatient insulin dependence, or DM diagnosis with related comorbidities | |
| Possible comorbidities: | |
| • Nerve damage (neuropathy): diabetic neuropathy | |
| • Kidney damage (nephropathy): CKD | |
| • Eye damage (retinopathy): diabetic retinopathy | |
| • PVD | |
| • DM-related amputation | |

CKD, chronic kidney disease; PVD, peripheral vascular disease.

Ryan-Einot-Gabriel-Welsch multiple range test to evaluate for significant differences between donor age, endothelial cell density, and death to preservation times. We also performed the Pearson $\chi^2$ test to compare categories of presumed low risk (1–3) versus categories of presumed high risk (4–5) to compare the occurrences of graft preparation failures. Two-sided $P$ values were considered statistically significant when less than 0.05. Descriptive statistics are reported as mean with SDs, and 95% confidence intervals (CI) are presented where appropriate.

## RESULTS

A total of 125 donor histories and associated tissue processing events were reviewed. Table 2 summarizes the diabetic donor scores, the rates of failure, and odds ratios. One hundred and seven diabetic grafts were successfully prepared and 18 procedures failed, representing a 14.4% failure rate for all attempts of DM tissue. Donors with a score of 1 (n = 9) were found to have an 11.1% failure rate (n = 1). DMEK donor tissue with a score of 2 (n = 25) had no graft failures for a 0% graft failure preparation rate. DMEK tissue with a score of 3 (n = 29), 4 (n = 20), and 5 (n = 25) had a 6.5% (n = 2), 16% (n = 4), and 30.6% (n = 11) graft preparation failure rate, respectively.

Logistic regression analysis was performed using the binary coded risk categories to assess statistically significant differences in the odds for graft preparation failures. Our initial odds for graft failure in the entire cohort was 0.168. The overall regression model was significant ($\chi^2(4) = 15.99$, $P = 0.003$). Risk category 1 showed a decrease in the odds of graft failure by a factor of 0.284 (95% CI, 0.03–2.56), risk category 2 had no occurrences of failure, and risk category 4 showed a decrease in the odds of graft failure by a factor of 0.45 (95% CI, 0.13–0.76). None in the aforementioned categories were found to be statistically significant (category 1: $P = 0.261$, category 2: $P = 0.998$, and category 4: $P = 0.23$). Risk categories 3 and 5, however, showed a significant decrease in the odds of graft failure by a factor of 0.16 and 0.44, respectively (category 3: 95% CI, 0.03–0.77, $P = 0.023$; category 5: 95% CI, −0.27 to 1.15, $P = 0.023$).

The Pearson $\chi^2$ test was also performed. We grouped our diabetic risk assessment categories into 2 groups indicating risk for graft preparation failure. Categories 1 to 3 represented low risk and were grouped together (group A). Categories 4 and 5 represented high risk and were grouped together (group B). In group A, there were 3 graft preparation failures and 62 successful preparations, and in group B there were 15 graft failures and 45 successful preparations. This difference was statistically significant ($\chi^2(1) = 10.518$; $P = 0.001$).

There was no statistically significant difference in donor death to preservation times between rating groups. There was a statistically significant difference found when comparing endothelial cell counts between rating 1 and ratings 3 and 5 ($P = 0.003$). There was also a statistically significant difference between donor ages ($P = 0.021$) between rating group 1 and rating groups 3, 4, and 5. The tissue parameters for all categories are summarized in Table 3.

## DISCUSSION

Published studies suggest that donors with a history of DM should be avoided to improve the likelihood of successful DMEK graft preparation.[11,12] With a relatively low volume of DMEK grafts in 2013, the exclusion of diabetic donors from the DMEK donor pool did not adversely affect tissue distribution. This has changed quickly with a dramatic increase in the number of tissues requested for DMEK in 2014.[2] This is especially important at our center where tissue distributed for DMEK has supplanted DSAEK to treat recipients with a diagnosis of Fuchs dystrophy. The total exclusion of all diabetic donors in addition to other tissue parameters could potentially create severe shortages in tissue availability if DMEK continues its dramatic increase in popularity.

There were several limitations to this study. First and foremost, once categorized, our numbers of tissues assigned to each DM severity category were not large. For example, with only 9 tissues assigned to category 1, only a single preparation failure resulted in a comparatively high preparation failure rate of 11.1%. Additionally, the analysis was performed over a wide date range, which included tissues prepared before and after the identification of DM as a risk factor for graft preparation by Greiner et al.[11] The result of this extended date range is that there may have been selection bias against choosing diabetic donors in the later months, and our learning curve with DMEK tissue preparation was potentially still in evolution.

**TABLE 2.** Diabetes Risk Categorization and Failure Rates

| | DM Rating | | | | | |
|---|---|---|---|---|---|---|
| | **1** | **2** | **3** | **4** | **5** | **Total** |
| Pass | 8 | 25 | 29 | 20 | 25 | 107 |
| Fail | 1 | 0 | 2 | 4 | 11 | 18 |
| Total | 9 | 25 | 31 | 24 | 36 | 125 |
| % of DM pool | 7.2 | 20 | 24.8 | 19.2 | 28.8 | 100 |
| Failure, % | 11.1 | 0.0 | 6.5 | 16.7 | 30.6 | 14.4 (average) |
| Odds ratio | Decreased by a factor of 0.28 | * | Decreased by a factor of 0.16 | Decreased by a factor of 0.45 | Decreased by a factor of 0.44 | Odds ratio for graft failure for entire cohort: 0.168 |
| Odds ratio $P$; 95% CI | 0.261; 0.03–2.56 | 0.998;* | 0.023; 0.03–0.77 | 0.23; 0.13–0.76 | 0.023; −0.27 to 1.15 | — |

*Odds for failure could not be generated because of lack observed failures.

**TABLE 3.** Donor Tissue Parameters for Each DM Risk Category

| DM Rating | Average Age | ECD | D-P (h:min) |
|---|---|---|---|
| 1 | 60.1 ± 7.4* | 2995 ± 309 | 9:14 ± 6:03 |
| 2 | 64.4 ± 5.7 | 2776 ± 261 | 9:40 ± 4:52 |
| 3 | 67.2 ± 6.1 | 2639 ± 258* | 11:20 ± 4:02 |
| 4 | 65.5 ± 6.4 | 2716 ± 255 | 11:34 ± 4:45 |
| 5 | 66.5 ± 5.1 | 2674 ± 202* | 11:48 ± 4:48 |
| Combined | 65.6 ± 6.1 | 2717 ± 260 | 11:01 ± 4:44 |

*Indicates of statistically significant lower value compared with group means.
ECD, endothelial cell density; D-P, death to preservation time.

Despite these limitations, we did find a statistically significant difference in the odds of graft failures within the categorizations of DM severity and a statistically significant logistical regression model. Although this is likely not yet a perfect model, this suggests that categorically ranking donors by diabetes and associated ailments can help eye banks avoid tissue wastage. The most limiting factor of this model is the low occurrence of graft preparation failure events overall. To perfect the model we would need to observe more failure events and use tissue that we believe would have a higher risk of failure. In this data series, donor tissue given the categorical ranking of 5 was found to be statistically significant with respect to the odds of preparation failure rates and showed the most frequent occurrence of graft preparation failures (30.6%). Category 4 was not found to be statistically significant but did have the second highest rate of graft failures (16.7%). For our categorizing scheme, categories 1 to 3 only had 3 of the 18 graft preparation failures that occurred in the entire cohort. It is important to point out that category 3 did show statistical significance for graft failures, but it was at a rate of 6.5%, well below the average of 14.4%. This may indicate that tissues categorized as 1 to 3 are relatively safe to prepare for DMEK and tissue categorized as 4 or 5 are more hazardous and likely to fail. In fact, when we combined categories 1 to 3 and 4 and 5 for a comparison, we did find a strong statistically significant difference between the occurrences of graft failures. This finding is in agreement with the publication of Vianna et al,[12] which showed that the duration of diabetes and comorbidities increases preparation failure.

We have shown that DMEK tissue preparation may be performed with a higher degree of confidence from tissues that are obtained from donors without evidence of severe DM and its associated comorbidities. The preparation failure rate of 4.6% in patients with mild DM as rated on our novel scale (ratings 1–3) compares well with the published DMEK preparation failure rate of 1.9% in donors without a known diagnosis of DM, as reported by Greiner et al.[11] The scale we developed is simple and easy to apply with information routinely gathered during the donor screening and eligibility release process. Our current practice is to routinely apply this scale to all diabetic donors, and our staff easily incorporated the tool into daily practice. We strive to maintain a responsible balance between available tissue and successful DMEK preparation. As diabetes prevalence continues to escalate in the United States and globally[15,16] along with DMEK surgery itself, the necessity of including some donors with diabetes will become increasingly unavoidable.

The total diabetes prevalence in the United States has increased from 9.8% to 12% to 14% of adults between the years 1998 and 2012 and a greater than 50% increase in global diabetes prevalence between 2000 and 2030 is anticipated.[15,16] Diabetes prevalence is highest in individuals older than 65 years, with a 33% prevalence, which may disproportionately affect our DMEK donor pool.[15] These data are stark reminders of the global health crisis that diabetes poses to our population. This crisis has spilled over into the world of corneal transplantation in an unexpected way with the advent of DMEK. This astounding prevalence of disease is seen in our DMEK donor pool. Assuming that the DM ratings remain constant beyond our sample size of 125 donors, this DM rating scale is expected to allow the use of half the diabetic donors who would normally have been excluded. At our eye bank, this increases the total DMEK tissue pool by approximately 25%.

This tool could be used by surgeons who peel their own DMEK grafts when assessing which tissue to prepare. As they are preparing their tissue just before surgery, a preparation failure would be more devastating than the failure of tissue prepared at an eye bank, where a replacement tissue is more likely to be readily available. The scale's utility for surgeons may be quite different when assessing preparation failure because some surgeons may elect to use torn grafts that eye banks would likely not release for transplantation.[9,17,18]

We anticipate that our rating scale could be further refined and enhanced with additional research. A better understanding of the risks associated with regard to each comorbidity would allow for a linear risk index. Speculation about the utility of serial hemoglobin $A_{1c}$ (HbA1c) measurements and their ability to quantify a true risk index is but one example of a rich area for future scientific investigation. Postmortem HbA1c measurements may also be of use to identify donors with undiagnosed DM. Data indicate that 11% to 36% of the current patients with diabetes are undiagnosed, suggesting that regardless of donor screening, our donor pool will likely contain diabetic donors, further emphasizing the need to carefully consider risk stratification of donors.[19] Unfortunately, the reality in the eye bank is that we do not have routine access to serial HbA1c data. Until we are able to further refine our understanding of which donor tissues tend to have fragile, sticky, and unyielding membranes for DMEK preparation, and identify those tissues before graft preparation, we are compelled to use the best information available to us. To our knowledge, this is the only tool available to aid eye banks to improve tissue selection for DMEK by including diabetic tissue without unduly increasing the risk of preparation failure.

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