Published in final edited form as:

Ophthalmology. 2015 March ; 122(3): 448–456. doi:10.1016/j.ophttha.2014.09.012.

The Effect of Donor Diabetes History on Graft Failure and Endothelial Cell Density Ten Years after Penetrating Keratoplasty

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Abstract

Objective—To examine the long term effect of donor diabetes history on graft failure and endothelial cell density (ECD) after penetrating keratoplasty (PKP) in the Cornea Donor Study

Design—Multi-center prospective, double-masked, controlled clinical trial

Participants—1090 subjects undergoing PKP for a moderate risk condition, principally Fuchs' dystrophy or pseudophakic/aphakic corneal edema (PACE), were enrolled by 105 surgeons from 80 clinical sites in the United States.

Methods—Corneas from donors 12 to 75 years old were assigned by 43 eye banks to participants without respect to recipient factors. Donor and recipient diabetes status was determined from existing medical records. Images of the central endothelium were obtained preoperatively

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Conflict of Interest: Francis Price, Jr., MD serves as a consultant for Allergan, Ophtec, and Staar and receives lecture fees from Alcon, Bausch & Lomb, Oculus and Santen. Mark Soper is employed by the Indiana Lions Eye & Tissue Transplant Bank. Alan Sugar received grant support from University of Michigan. Mark Terry receives educational grant support from Moria and educational grant support and royalties from Bausch & Lomb.

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(baseline) and at intervals for ten years postoperatively and analyzed by a central image analysis reading center to determine ECD.

Main Outcome Measure(s)—Time to graft failure (regraft *or* cloudy cornea for 3 consecutive months) and ECD.

Results—There was no statistically significant association of donor diabetes history with 10-year graft failure, baseline ECD, 10-year ECD or ECD values longitudinally over time in unadjusted analyses nor after adjusting for donor age and other significant covariates. The 10-year graft failure rate was 23% in the 199 cases receiving a cornea from a donor with diabetes versus 26% in the 891 cases receiving a cornea from a donor without diabetes (95% confidence interval for the difference: -10% to +6%; unadjusted $p = 0.60$). Baseline ECD ($p=0.71$), 10-year ECD ($p>0.99$), and changes in ECD over 10 years ($p=0.86$) were similar comparing donor diabetes and no-diabetes groups.

Conclusions and Relevance—The study results do not suggest an association between donor diabetes and PKP outcome. However, the assessment of donor diabetes was imprecise and based on historical data only. The increasing frequency of diabetes in the aging population in the United States affects the donor pool, thus the impact of donor diabetes on long term endothelial health after penetrating and/or endothelial keratoplasty warrants further study with more precise measures of diabetes and its complications.

Trial Registration—clinicaltrials.gov NCT00006411

Introduction

Numerous animal and human studies have suggested that the corneal endothelium is adversely affected biochemically,^{1–5} morphologically,^{6–13} and functionally^{8, 13–21} by diabetes mellitus. Despite this literature, there have been virtually no studies on the effects of diabetes in cornea donors on graft outcome and cell loss following keratoplasty. In a study of organ culture stored corneas at 31°C, diabetes in the donor did not affect endothelial cell loss in storage for < 30 days compared with non-diabetic donor tissue²². Some medical directors and surgeons are reluctant to use donor corneas from diabetic donors particularly when associated with complications from diabetes (e.g, laser or anti-vascular-endothelial-growth-factor-treated retinopathy, peripheral vascular disease) and/or lower endothelial cell density (ECD) around the minimum ECD of 2000 cells/mm² associated with significant polymegathism and pleomorphism. However, no studies to our knowledge have examined the effect of diabetes determined historically in donor corneas stored at 4°C.

The dearth of information on diabetes in the donor has occurred in part because the Medical Standards and Procedures Manual of the Eye Bank Association of America (EBAA) does not require tracking of diabetes as a separate category contributing to donor death.²³ Instead, each eye bank and its medical director determine what data are recorded from the donor's medical history, including diabetes and complications associated with this disease (retinopathy, nephropathy, neuropathy, vascular disease). In this regard, scanning a write-in field for any comments regarding diabetes utilizing the Midwire software of Midwest Eye-Banks for 5 eye banks in 2013, 6,704 out of 22,105 eyes retrieved (30%) were from donors

with diabetes, having an average age of 62 (personal communication, Michael O'Keefe). Of these 22,105 eyes, 13,164 (60%) were suitable for transplant with a comparable percentage between the donors with and without diabetes. Of the 13,164 suitable donors, 3,757 donors with diabetes (29%) were used for keratoplasty, either penetrating or endothelial. This figure is consistent with the Centers for Disease Control and Prevention (CDC) report that 26% of people 65 years of age in 2012 had diabetes.²⁴ Given the tremendous growth of diabetes in the population, morphologic and functional data suggesting that the diabetic corneal endothelium is abnormal, it is incumbent upon the fields of eye banking and corneal surgery to determine if our patients are at increased risk of graft failure when receiving corneas from donors with diabetes. To address this issue, we utilized the dataset from the Cornea Donor Study (CDS) to evaluate the effect of the donor's diabetes status on graft outcome and on central corneal endothelial cell density (ECD) at baseline and longitudinally over 10 years.

Materials and Methods

Complete details of the CDS and Specular Microscopy Ancillary Study (SMAS) protocols have been previously reported^{25–27}; pertinent aspects are described here briefly. The CDS is registered as a clinical trial through the Clinical Trials Registry of the National Institutes of Health (NCT00006411) and information is publically available (<http://www.clinicaltrials.gov>, accessed 05/16/13). The study protocol was approved by the institutional review board at each investigational site, and individual participants gave written informed consent to participate in the study. Eligible donor corneas met EBAA standards for human corneal transplantation. Assigned corneas were from donors 12 to 75 years old with an eye bank measured central ECD between 2300 and 3300 cells/mm². The eye bank reported at the time of collection whether or not the donor had a history of diabetes, but no information regarding type, duration, medications, metabolic control, complications, or obesity was captured.

Between January 2000 and August 2002, 1090 eligible patients (median age 72 years, quartiles 65, 76 years) at 80 sites had a PKP for Fuchs' dystrophy (62%), pseudophakic/aphakic corneal edema (PACE) (34%; 93% pseudophakic and 7% aphakic) or another corneal endothelial disorder (4%). Similar to the donor diabetes information, the presence of recipient diabetes was recorded, but type, duration, medications, metabolic control, complications or obesity were not captured. Clinical investigators and participants were masked to all characteristics of the donor cornea including age, diabetes history and ECD. Preoperative management, surgical technique, and postoperative care, including prescription of medications, were provided according to each investigator's routine. The minimum follow-up visit schedule included visits at 6 months, 1 year and then annually for 10 to 12 years for those participants who did not require a regrant. Graft clarity was assessed at each visit. The definition of graft failure, based on the definition used in the Collaborative Corneal Transplantation Studies (CCTS)²⁸, was a regrant or, in the absence of regrant, a cloudy cornea in which there was loss of central graft clarity sufficient to compromise vision for a minimum of three consecutive months.

A subset of the CDS participants also consented to participate in the SMAS.^{29, 30} Baseline preoperative donor images and postoperative recipient images obtained at the 6-month and

annual follow-up visits were evaluated for quality and ECD by a central reading center, the Cornea Image Analysis Reading Center (CIARC; formerly the Specular Microscopy Reading Center) at Case Western Reserve University and University Hospitals Eye Institute, using a variable frame analysis method. Details of CIARC procedures have been previously described for donor and post-operative images^{29–32}, including reader training and certification, image quality grading, image calibration, variable frame analysis for ECD determination, and adjudication procedures for image quality and ECD determination.

Statistical Methods

Cumulative probabilities of graft failure (subsequently referred to as “graft failure rates”) at 10 years along with 95% confidence intervals were calculated using the Kaplan-Meier method. Univariate comparisons of the 10 year graft failure rate were performed using a normal approximation with the standard error estimated using Greenwood’s formula. Multivariate analysis was performed using the Cox proportional hazards model adjusting for donor age and donor race as possible confounders (both $p < 0.10$). The proportional hazards assumption was assessed using a Kolmogorov-type supremum test^{33, 34} with 1000 simulated patterns. This assumption was violated for donor age, so the baseline hazard function was stratified by donor age. Effect modifications of donor diabetes history on graft failure were assessed for recipient diagnosis, recipient diabetes history, recipient age, donor age, donor race and baseline ECD.

Cross-sectional regression models were used to assess the association of donor diabetes history with ECD at baseline and at 10-years. All 1090 subjects were included in the analysis of baseline ECD while only 176 subjects with a surviving graft and a gradable image at 10 years were included in the analysis of 10-year ECD. For cases in which the baseline donor specular endothelial image was not analyzed by the CIARC (N=432), the ECD determined by the eye bank was used. Baseline analysis investigated possible effect modification of donor diabetes by recipient diagnosis, recipient diabetes history, recipient age, donor age and donor race. Corresponding subgroup analyses were not performed on the 10 year ECD data due to the small sample size (N=176).

To assess the association of donor diabetes history with ECD during follow-up with measurements taken at 6 months, 1, 2, 3, 4, 5, 7/8 and 10 years, a fixed effects longitudinal model was fit by restricted maximum likelihood (REML) using an unstructured covariance matrix to account for correlated data. Analysis was restricted to images taken prior to graft failure and included 2344 images from 591 subjects. Therefore, both the 10-year and the longitudinal analyses were conditional on graft survival since only the images obtained prior to graft failure were included. Longitudinal analysis investigated possible effect modifications of donor diabetes by recipient diagnosis, recipient diabetes history, recipient age, donor age and donor race.

All the ECD models were adjusted for possible confounding with donor age and donor race by including these factors whenever $p < 0.10$. The 10-year and the longitudinal model were also adjusted for baseline ECD. QQ-plots revealed that the ECD values were not normally distributed; therefore, in all of the models, rank scores transformed to have a normal

distribution (van der Waerden scores) were used as the dependent variable.^{29, 30} Continuous covariates in the models were also transformed in the same manner.

For all multivariate models (graft failure and ECD), missing values for covariates were treated as a separate category for discrete variables and a missing value indicator was added for continuous variables. All reported p-values are two-sided. Statistical analyses were conducted using SAS version 9.3 software (SAS Institute Inc., Cary, NC).

Results

Baseline Characteristics

Among the 1090 cases, 199 (18%) received a cornea from a donor with a history of diabetes while 891 (82%) did not. As expected, a history of diabetes was more likely in older donors (91% of donors with a history of diabetes were at least 50 years of age versus 76% of donors who did not have a history of diabetes; Table 1). Primary cause of death also varied somewhat by diabetes status, reflecting this age difference, with higher cardiac and stroke death occurrence in the diabetic donor group. Other donor factors including procurement, and slit-lamp characteristics were well balanced between donor diabetes history groups (Table 2).

Recipient characteristics also were well-balanced between cases with a donor with diabetes and cases with a donor without diabetes, including age, gender, race, diabetes, diagnosis, lens status and glaucoma history. Of the 1090 recipients, 141 (13%) had known diabetes, 899 (82%) did not have known diabetes, and 50 (5%) had unknown diabetes status. Twenty-eight of the 141 diabetic recipients (20%) received a cornea from a diabetic donor.

Graft Failure

The 10-year graft failure rate was 23% in the 199 cases receiving a cornea from a donor with diabetes versus 26% in the 891 cases receiving a cornea from a donor without diabetes (95% confidence interval for the difference: -10% to +6%; p-value for the difference at 10 years =0.60; Figure 1). There was also no detectable effect of donor diabetes history in the multivariate analysis adjusting for donor race and stratifying by donor age (p=0.14). Comparisons of graft failure rates in cases receiving corneas from donors with and without a history of diabetes were similar in subgroups by recipient diabetes history (recipient had diabetes: 25% versus 23%; recipient did not have diabetes: 22% versus 25% respectively) and recipient diagnosis (Fuchs': 17% versus 20%; PACE: 36% versus 37%, respectively). Additional subgroup analyses by recipient age, donor age, donor race and baseline donor ECD similarly found no effect modification of donor diabetes history (Figure 2).

Endothelial Cell Density

Median baseline ECD was 2618 cells/mm² (interquartile range [IQR] 2445 to 2864 cells/mm²) in cases receiving a cornea from a diabetic donor versus 2671 cells/mm² (IQR 2462 to 2874 cells/mm²) in cases receiving a cornea from a non-diabetic donor (unadjusted p=0.15, p-value adjusted for donor age =0.71). No associations were apparent in subgroups based on recipient diabetes history, recipient diagnosis, recipient age and donor age (Table

3). There was a trend toward lower ECD among non-White donors ($p=0.05$ uncorrected for multiple comparisons), but the number of non-White donors with diabetes was small ($N=15$).

Likewise, for the 176 participants with a surviving graft and a gradable image at 10 years, there was no significant difference in 10-year ECD by donor diabetes history (median 570 cells/mm², IQR 493 to 774 cells/mm² for corneas from donors with diabetes versus median 622 cells/mm², IQR 502 to 764 cells/mm² for corneas from non-diabetic donors; Table 3; unadjusted $p=0.40$, p -value adjusted for donor age and baseline ECD >0.99).

In the longitudinal analysis incorporating follow-up measurements through 10 years, there was no overall effect of donor diabetes history after adjusting for donor age and baseline ECD (Figure 3; $p=0.86$) and no associations in subgroups based on recipient diabetes history, recipient diagnosis, recipient age, donor age and donor race (Table 3).

Discussion

In an analysis of the CDS, we found that a history of diabetes in the donor did not adversely affect graft survival or ECD following PKP performed primarily for Fuchs' dystrophy or pseudophakic/aphakic corneal edema. These findings are reassuring given the dramatically increased prevalence of diabetes in the donor pool between 2000 – 2002 (18% in this study) and 2013 (29%, Midwire database, personal communication, Michael O'Keefe). We believe that this 61% increase in diabetes over the past decade between these historically determined donor populations is influenced by: a dramatic increase in diabetes, diagnosed and undiagnosed in the population as a whole; the strong association between cardiovascular disease and stroke associated with diabetes leading to a higher mortality rate; and the increasing use of older donor tissue.

Interpretation of our results is tempered by a limited determination for presence of donor diabetes by the CDS eye banks. If there is a subset of donors with diabetes who were poorly controlled or had associated significant ocular and/or systemic complications (e.g., retinopathy, neuropathy, nephropathy, peripheral vascular disease), that could be reflective of a generalized deleterious effect on cells in diabetes, this subset may have a compromised corneal endothelium subject to a higher percentage of graft failures and/or endothelial cell loss. Unfortunately our data set was insufficiently informed to detect this effect. Nevertheless, we found no significant association between donor diabetes and graft failure or endothelial cell loss. The apparent lack of an adverse effect of donor diabetes is reassuring given the sizable literature suggesting that the corneal endothelium in diabetes is affected biochemically^{1–5}, morphologically^{6–13}, functionally^{8, 13–21} and clinically at least with cataract surgery^{35–38} and may possibly cause a recipient effect in PKP³⁹. The biochemical and pathophysiologic effects of chronic hyperglycemia on the endothelium are compelling evidence of potential for cell damage in diabetes. One author has suggested that high glucose levels in the tear film and aqueous humor result in the accumulation of intracellular sorbitol and disruption of Na⁺ handling³, affecting the endothelial pump. Another author has examined the corneal redox state and found significant changes in the diabetic corneal endothelium⁵. Finally, the accumulation of advanced glycation end

products, oxidative stress and nuclear factor kappa-B in diabetes have been found to advance endothelial apoptosis.¹

Studies examining endothelial barrier and pump functions have had mixed results with some showing increased endothelial permeability in diabetes^{13, 16}, while others have found no effect on endothelial permeability in this population^{7, 8, 20}. Corneal stress studies with induced hypoxia have shown delayed recovery in diabetes.^{15, 17, 18, 21} Morphologic studies comparing the endothelium in diabetes to age matched controls have consistently found morphometric differences in coefficient of variation and % of hexagonal cells.^{6–8, 13, 40, 41} Some studies noted a lower ECD^{9, 10, 42}, and in some studies have related these changes to duration of diabetes⁹ HbA1c levels and degree of retinopathy¹⁰.

Numerous studies of cataract surgery^{35–38} comparing diabetic patients with normal controls have shown differences in morphologic and corneal thickness recovery in the diabetic group, emphasizing that this population of endothelial cells is under stress. One PKP study showed a significantly higher graft failure rate at 5 years in recipients with diabetes compared to recipients without diabetes (5.7% vs. 2.4%); the effect of donor diabetes was not examined.³⁹ Interestingly, in our study the presence of diabetes in both the donor and recipient did not adversely affect graft outcome, although this group was small (n = 28). We also did not note a greater effect of graft failures and cell loss associated with donor age, even in the group where age had the greatest effect (>71 to 75 years of age) on graft failures and cell loss.

The adhesive quality of Descemet's membrane to the overlying stroma may also be altered in donor corneas from individuals from diabetes. Greiner et al reviewed 359 donor corneas prepared for Descemet's membrane endothelial keratoplasty (DMEK) surgery and found that the 114 diabetic donors had a 9-fold increased risk of destruction by tearing during the pre-stripping process.⁴³ They attributed this increased risk of Descemet's membrane tearing in diabetic donors to an increase in the adhesive glycoproteins present in the interfacial matrix between Descemet's membrane and the posterior stroma.⁴⁴ An increasing number of surgeons are switching from Descemet's stripping endothelial keratoplasty (DSEK) to performing DMEK surgery for the treatment endothelial dysfunction because of DMEK's possibly improved visual results and lower graft rejection rates, so the role of diabetic donors in keratoplasty is likely to increase in clinical relevance.

In conclusion, with 1) the increasing donor population with diabetes; 2) conflicting results between our reassuring findings in PKP in regards to graft success and endothelial cell loss in donors with or without diabetes defined historically compared with laboratory, *in vivo* endothelial imaging, functional studies, and the cataract surgery studies, showing a possible deleterious effect; 3) a reluctance on some surgeons and medical directors to use donors from diabetes, particularly associated with ocular and/or systemic complications, and 4) the growth of endothelial keratoplasty (DSEK, DMEK) with its demands on the donor cornea physically and functionally, a clinical trial examining the effect of diabetes in the donor in a more precisely defined manner on graft success and endothelial changes following endothelial keratoplasty may be warranted to assure a healthy donor pool with advances in keratoplasty.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial Support: Supported by cooperative agreements with the National Eye Institute, National Institutes of Health, Department of Health and Human Services EY12728 and EY12358. Additional support provided by: Eye Bank Association of America, Bausch & Lomb, Inc., Tissue Banks International, Vision Share, Inc., San Diego Eye Bank, The Cornea Society, Katena Products, Inc., ViroMed Laboratories, Inc., Midwest Eye-Banks (Michigan Eye-Bank, Illinois Eye-Bank, Cleveland Eye Bank and Lions Eye Bank of New Jersey), Konan Medical Corp., Eye Bank for Sight Restoration, SightLife, Sight Society of Northeastern New York (Lions Eye Bank of Albany), Lions Eye Bank of Oregon

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CORNEA DONOR STUDY INVESTIGATOR GROUP

Listed in order of number of participants enrolled in the Cornea Donor Study are the clinical sites with city, state, site name, number of participants in parentheses, and names of the investigators ordered alphabetically that participated in the study as part of the CDS Investigator Group by enrolling or following participants. The names of the coordinators ordered alphabetically that participated in the extended follow-up phase of the study are also included.

CLINICAL SITES

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Listed in order of number of patients enrolled in the Cornea Donor Study are the eye banks with eye bank name, city, state, number of patients in parentheses and names of the eye bank directors and coordinators who participated in the study during the enrollment phase (D=Director, C=Coordinator).

EYE BANKS

Midwest Eye-Banks (192) [Ann Arbor, MI; Michigan Eye Bank, (145); Chicago, IL; Illinois Eye Bank, (47)]: Florence M. Johnston (D), Kyle L. Mavin (C), Kristen E. McCoy (C), Michael B. O'Keefe (C) *Tissue Banks International (119) [Boston, MA; New England Eye & Tissue Transplant Bank (47); Indianapolis, IN; Indiana Lions Eye & Tissue Transplant Bank (22); Bismarck, ND; Lions Eye Bank of North Dakota, Inc. (19); Dayton, OH; Lions Eye Bank of West Central Ohio (11); Baltimore, MD; Medical Eye Bank of Maryland & Washington Eye Bank (4); Santa Ana, CA; Orange County Eye & Tissue Bank (4); Albuquerque, NM; New Mexico Lions Eye Bank (3); Los Angeles, CA; Doheny Eye and Tissue Transplant Bank (3); Orlando, FL; Medical Eye Bank of Florida (2); Oakland, CA; Northern California Transplant Bank (2); Springfield, NJ; Lions Eye Bank of New Jersey (2)]:* Gerald J. Cole, MBA (D), Diane F. Johnston (C), Mark A. Jones (C), Sameera M. Farazdaghi, MPH (C), Elizabeth N. Walunas (C) *Seattle, WA; SightLife (86):* Monty M. Montoya, MBA (D), Bernie Iliakis (C), Rick D. McDonald (C), Misty L. Ostermiller (C), Cathy E. Saltwick (C) *Tampa, FL; Central Florida Lions Eye & Tissue Bank, Inc. (73):* Jason K. Woody (D, C) *Allentown, PA; Northeast Pennsylvania Lions Eye Bank, Inc. (70):* Mark H. Weaver (D), Michael J. Christ (C), Mark B. Gross (C) *Minneapolis, MN; Minnesota Lions Eye Bank (61):* Carol R. Engel (D), Raylene A. Dale (C), Stephanie K. Hackl (C), Elena J. Henriksen (C), Kathryn J. Kalmoe (C), Jennifer M. Larson (C), Jackie V. Mallin (C), Brian J. Philippy (C) *Albany, NY; Sight Society of Northeastern New York (58):* Maryann Sharpe-Cassese, RN, MSN (D), Sue M. Hayes (C) *Philadelphia, PA; Lions Eye Bank of Delaware Valley (58):* Robert E. Lytle (D), David A. Rechtshaffen (C) *Atlanta, GA; Georgia Eye Bank, Inc. (57):* Bruce Varnum (D), Erin B. Angel (C), Matt D. Durell (C), Teresa R. Williams (C) *Cleveland, OH; Cleveland Eye Bank (45):* Susan V. Janssen (D), Brian E. Kraus (C), Marcy B. McLain (C), Jackie A. Rossi (C) *Dallas, TX; Transplant Services Center UT Southwestern (33):* Ellen L. Heck, MS, MA (D), Marilyn S. Hayes (C) *Phoenix, AZ; Donor Network of Arizona (28):* Gregory C. Davis (D), Tara L. Chavez (C), Lori D. Oswald (C), Noreen B. Ruiz (C) *San Diego, CA; San Diego Eye Bank (26):* Jeffrey G. Penta, MBA (D), Wayne E. Dietz (C), Jennifer L. Nary (C) *Charleston, WV; Medical Eye Bank of West Virginia (21):* Kenneth R. Sheriff (D), Nancy C. Driver (C) *Charlotte, NC; Lifeshare of the Carolinas (21):* William J. Faircloth (D), Paul E. Williams (C) *Winston-Salem, NC; The North Carolina Eye Bank, Inc. (21):* Kurt Weber, MA, MBA (D), Jerry W. Barker (C), Donna M. Bridges (C), Lee Chenier (C), Mark Soper (C) *Redlands, CA; Inland Eye & Tissue Bank (20):* Betsy Allen (D), Samantha J. Wright (C) *Louisville, KY; University of Louisville Lions Eye Bank (16):* James R. Martin (D), Anne J. Watson (C) *Sacramento, CA; Sierra Eye & Tissue Donor Services-DCI (15):* Greg McDonough, MS (D), Kristel D. Beilby (C) *Rochester, NY; Rochester Eye & Human Parts Bank, Inc. (13):* Linda K. Fraser (D), Tammi S. Sharpe (C) *Pittsburgh, PA; Center for Organ Recovery and Education (11):* Robert C. Arffa, MD, Michael A. Tramber (C) *Portland, OR; Lions Eye Bank of Oregon (10):* Barbara L. Crow (D), Matthew M. Fisher (C), Chris G. Stoeger (C) *Aurora, CO; Rocky Mountain Lions Eye Bank (9):* Edmund Jacobs (D), Michael P. Filbin (C), James I. Mather (C), Christopher M. McGriff (C), Eric E. Meinecke (C) *Iowa City, IA; Iowa Lions Eye Bank (9):* Patricia J. Mason (D), Garret D. Locke (C), Janice F. Reiter (C) *Norfolk, VA; Lions Medical Eye*

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Figure 1. Graft Failure over Time According to Donor Diabetes History

The table beneath the figure presents the number of subjects at risk in the beginning of each year along with the number of graft failures, deaths, losses to follow-up, and censored subjects during the year.

* Test for effect modification with donor diabetes history and the indicated factor. Donor age, baseline ECD and recipient age were analyzed as continuous factors.

† There were 50 patients with unknown diabetes history and 45 patients with 'other' diagnoses

Figure 2.
Association of Donor Diabetes History and Graft Failure within Subgroups

Figure 3. ECD over Time According to Donor Diabetes History

In the box plot, black dots indicate mean values; horizontal lines in the boxes, medians; and the bottom and top of the boxes, the 25th and 75th percentiles.

Table 1

Donor Factors by Donor Diabetes History (N=1090)

Donor Factors	Donor Diabetes History			
	No N=891		Yes N=199	
	N	%	N	%
Age (years)				
<50	218	24%	18	9%
50 – <66	376	42%	95	48%
66	297	33%	86	43%
<i>mean ± SD</i>		57 ± 15		62 ± 10
Gender				
Female	302	34%	72	36%
Male	589	66%	127	64%
Race				
White	840	94%	184	92%
African-American	31	3%	10	5%
Hispanic	10	1%	1	<1%
Asian	3	<1%	0	0
Other	7	<1%	4	2%
Cause of Death				
Cardio/Stroke	512	57%	147	74%
Cancer	185	21%	22	11%
Trauma	90	10%	6	3%
Respiratory	59	7%	19	10%
Other	45	5%	5	3%
ABO/Rh Match to Recipient				
Missing	147	16%	30	15%
Yes	400	45%	94	47%
No	344	39%	75	38%
Gender Match to Recipient				
Both Female	198	22%	44	22%
Both Male	220	25%	41	21%
No Match	473	53%	114	57%
Type of Tissue Retrieval				
Enucleation	179	20%	39	20%
In situ	712	80%	160	80%
Tissue Refrigerated				
No	209	23%	46	23%
Yes	682	77%	153	77%
Time from Death to Preservation (hours)				
<4	166	19%	29	15%

Donor Factors	Donor Diabetes History			
	No N=891		Yes N=199	
	N	%	N	%
4 – <8	473	53%	105	53%
8 – <10	128	14%	41	21%
10	124	14%	24	12%
Time from Death to Surgery				
4 days	609	68%	134	67%
>4 days	282	32%	65	33%

Table 2

Donor Cornea Factors by Donor Diabetes History (N=1090)

Donor Cornea Characteristics	Donor Diabetes History			
	No N=891		Yes N=199	
	N	%	N	%
Baseline ECD (cells/mm²)				
<2500	260	29%	58	29%
2500 – <2700	211	24%	59	30%
2700 – <3000	302	34%	59	30%
3000	118	13%	23	12%
<i>median (quartiles)</i>	2671 (2462, 2874)		2618 (2445, 2864)	
Polymorphism/Polymegathism				
None	781	88%	170	85%
Mild/moderate	110	12%	29	15%
Endothelial Cell Damage-Central				
None	889	>99%	198	>99%
Mild	2	<1%	1	<1%
Endothelial Cell Damage-Diffuse				
None	859	96%	195	98%
Mild/moderate	32	4%	4	2%
Endothelial Cell Damage-Peripheral				
None	847	95%	191	96%
Mild	44	5%	8	4%
Epithelium Defects				
Clear and intact	434	49%	91	46%
Defects on 50%	457	51%	108	54%
Epithelium Haze				
None	589	66%	144	72%
Mild	266	30%	49	25%
Moderate/severe	36	4%	6	3%
Epithelium-Exposure				
None	180	20%	29	15%
Mild	545	61%	116	58%
Moderate/severe	166	19%	54	27%
Stromal Edema				
None	664	75%	153	77%
Mild/moderate	227	25%	46	23%
Stromal Arcus				
None	319	36%	61	31%
Present	572	64%	138	69%
Descemet's Membrane Folds				

Donor Cornea Characteristics	Donor Diabetes History			
	No N=891		Yes N=199	
	N	%	N	%
None	304	34%	72	36%
Mild/moderate	587	66%	127	64%
Snail Tracks-Central				
None	822	92%	189	95%
Mild/moderate	69	8%	10	5%
Snail Tracks-Diffuse				
None	737	83%	166	83%
Mild/moderate	154	17%	33	17%
Snail Tracks-Peripheral				
None	713	80%	167	84%
Mild/moderate/severe	178	20%	32	16%
Donor Graft Size				
<8.0 mm	198	22%	46	23%
=8.0 mm	210	24%	55	28%
>8.0 mm	483	54%	98	49%

Table 3

ECD According to Donor Diabetes History

Baseline Model (N=1090)						
	Donor Diabetes History			P-value*		
	N	Baseline ECD median (quartiles)	No	Yes	Baseline ECD median (quartiles)	P-value*
Overall	891	2671 (2462, 2874)	199	2618 (2445, 2864)		
Recipient Diabetes History[†]						0.69
No	736	2670 (2448, 2874)	163	2618 (2444, 2834)		
Yes	113	2652 (2500, 2862)	28	2670 (2508, 2873)		
Recipient Diagnosis[‡]						0.10
Fuchs'	552	2668 (2442, 2873)	124	2655 (2490, 2846)		
PACE	298	2668 (2496, 2857)	71	2594 (2426, 2816)		
Recipient Age						0.86
<60 years	135	2670 (2487, 2894)	27	2695 (2397, 2959)		
60-<70 years	235	2646 (2428, 2842)	49	2577 (2445, 2794)		
70 years	521	2686 (2475, 2879)	123	2637 (2487, 2881)		
Donor Age						0.18
<50 years	218	2767 (2543, 2971)	18	2721 (2483, 2902)		
50 - <66 years	376	2658 (2443, 2870)	95	2603 (2439, 2829)		
66 years	297	2625 (2448, 2824)	86	2621 (2445, 2866)		
Donor Race						0.05
White	840	2668 (2459, 2874)	184	2627 (2472, 2861)		
Non-White	51	2679 (2551, 2878)	15	2550 (2166, 2959)		

10-Year Model (N=176)

10-Year Model (N=176)						
	Donor Diabetes History			P-value [‡]		
	N	10-Year ECD median (quartiles)	No	Yes	10-Year ECD median (quartiles)	P-value [‡]
Overall	149	622 (502, 764)	27	570 (493, 774)		
Recipient Diabetes History						NA

10-Year Model (N=176)						
	Donor Diabetes History					
	No			Yes		
	N	10-Year ECD median (quartiles)	N	10-Year ECD median (quartiles)	P-value [‡]	
No	134	616 (506, 762)	24	562 (493, 703)		
Yes	15	646 (454, 869)	3	NA		
Recipient Diagnosis^{§§}						
Fuchs'	125	613 (500, 758)	20	534 (483, 609)		NA
PACE	21	675 (589, 1094)	6	NA		
Recipient Age						
<60 years	46	675 (530, 846)	5	NA		NA
60–<70 years	48	623 (486, 912)	7	NA		
70 years	55	613 (493, 730)	15	570 (493, 860)		
Donor Age						
<50 years	51	688 (565, 942)	4	NA		NA
50–<66 years	59	606 (461, 760)	11	600 (472, 850)		
66 years	39	590 (480, 698)	12	513 (488, 562)		
Donor Race						
White	144	623 (504, 771)	25	570 (502, 774)		NA
Non-White	5	NA	2	NA		
Longitudinal Model (N=2344 images from 591 subjects)						
	P-value*					
Recipient Diabetes History[‡]						0.69
Recipient Diagnosis[‡]						0.43
Recipient Age			NA			0.90
Donor Age						0.09
Donor Race						0.91

* Test for effect modification with donor diabetes and the indicated factor. Continuous factors were used for donor age and recipient age.

[‡]Too few cases at 10 years for subgroup analyses.

[§]There were 50 patients with unknown diabetes history and 45 patients with "other" diagnoses at baseline.

^{§§}There were 4 patients with "other" diagnoses at 10 years.