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The Effect of Donor Diabetes History on Graft Failure and Endothelial Cell Density 10 Years after Penetrating Keratoplasty

*Jonathan H. Lass, MD,[1] Tonya D. Riddlesworth, PhD,[2] Robin L. Gal, MSPH,[2] Craig Kollman, PhD,[2] Beth A. Benetz, MA,[1] Francis W. Price, Jr., MD,[3] Alan Sugar, MD,[4] Mark A. Terry, MD,[5] Mark Soper,[6] Roy W. Beck, MD, PhD,[2] for the Cornea Donor Study Research Group**

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

Design: Multicenter, prospective, double-masked, controlled clinical trial.

Participants: One thousand ninety subjects undergoing PK for a moderate risk condition, principally Fuchs' dystrophy or pseudophakic or aphakic corneal edema, were enrolled by 105 surgeons from 80 clinical sites in the United States.

Methods: Corneas from donors 12 to 75 years of age 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 before surgery (baseline) and at intervals for 10 years after surgery and were analyzed by a central image analysis reading center to determine ECD.

Main Outcome Measures: 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 patients receiving a cornea from a donor with diabetes versus 26% in the 891 patients 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 groups with and without diabetes.

Conclusions: The study results do not suggest an association between donor diabetes and PK 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 PK or endothelial keratoplasty, or both, warrants further study with more precise measures of diabetes and its complications. *Ophthalmology 2015;122:448-456 © 2015 by the American Academy of Ophthalmology.*

*Supplemental material is available online at www.aaojournal.org.

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 after 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 fewer than 30 days compared with nondiabetic donor tissue.[22] Some medical directors and surgeons are reluctant to use donor corneas from diabetic donors particularly when associated with complications from diabetes (e.g., laser-treated or anti–vascular endothelial growth factor–treated retinopathy, peripheral vascular disease), with lower endothelial cell density (ECD) around the minimum ECD of 2000 cells/mm^2 associated with significant polymegathism and pleomorphism, or with both. 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 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

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write-in field for any comments regarding diabetes using the Midwire software of Midwest Eye Banks for 5 eye banks in 2013, 6704 (30%) of 22 105 eyes retrieved were from donors with diabetes, having an average age of 62 years (Michael O'Keefe, personal communication, 2014). 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, 3757 donors with diabetes (29%) were used for keratoplasty, either penetrating or endothelial. This figure is consistent with the Centers for Disease Control and Prevention report that 26% of people 65 years of age or older in 2012 had diabetes.[24] Given the tremendous growth of diabetes in the population and morphologic and functional data suggesting that the diabetic corneal endothelium is abnormal, it is incumbent on 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 used 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 ECD at baseline and longitudinally over 10 years.

Methods

Complete details of the CDS and Specular Microscopy Ancillary Study protocols have been reported previously[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 (identifier, NCT00006411; available at: http://www.clinicaltrials.gov; accessed May 16, 2013). 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 Eye Bank Association of America standards for human corneal transplantation. Assigned corneas were from donors 12 to 75 years of age with an eye bank–measured central ECD between 2300 and 3300 cells/mm^2. The eye bank reported at the time of collection regardless of whether 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 and 76 years) at 80 sites underwent PK for Fuchs dystrophy (62%), pseudophakic or aphakic corneal edema (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 regraft. Graft clarity was assessed at each visit. The definition of graft failure, based on the definition used in the Collaborative Corneal Transplantation Studies,[28] was a regraft or, in the absence of regraft, a cloudy cornea in which there was loss of central graft clarity sufficient to compromise vision for a minimum of 3 consecutive months.

Table 1. Donor Factors by Donor Diabetes History (n = 1090)

Donor Factors	Donor Diabetes History			
	No (n = 891)		*Yes (n = 199)*	
	No.	%	*No.*	%
Age (yrs)				
<50	218	24	18	9
50–<66	376	42	95	48
≥66	297	33	86	43
Mean ± SD	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				
Cardiovascular/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 (hrs)				
<4	166	19	29	15
4–<8	473	53	105	53
8–<10	128	14	41	21
≥10	124	14	24	12
Time from death to surgery (days)				
≤4	609	68	134	67
>4	282	32	65	33

SD = standard deviation.

A subset of the CDS participants also consented to participate in the Specular Microscopy Ancillary Study.[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 (formerly the Specular Microscopy Reading Center) at Case Western Reserve University and University Hospitals Eye Institute, using a variable frame analysis method. Details of Cornea Image Analysis Reading Center procedures have been described previously for donor and postoperative 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.