Donor diabetes mellitus is a risk factor for diminished outcome after liver transplantation: a nationwide retrospective cohort study

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ORIGINAL ARTICLE

Donor diabetes mellitus is a risk factor for diminished outcome after liver transplantation: a nationwide retrospective cohort study

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SUMMARY

With the growing incidence of diabetes mellitus (DM), an increasing number of organ donors with DM can be expected. We sought to investigate the association between donor DM with early post-transplant outcomes. From a national cohort of adult liver transplant recipients (1996–2016), all recipients transplanted with a liver from a DM donor ($n = 69$) were matched 1:2 with recipients of livers from non-DM donors ($n = 138$). The primary end-point included early post-transplant outcome, such as the incidence of primary nonfunction (PNF), hepatic artery thrombosis (HAT), and 90-day graft survival. Cox regression analysis was used to analyze the impact of donor DM on graft failure. PNF was observed in 5.8% of grafts from DM donors versus 2.9% of non-DM donor grafts ($P = 0.31$). Recipients of grafts derived from DM donors had a higher incidence of HAT (8.7% vs. 2.2%, $P = 0.03$) and decreased 90-day graft survival (88.4% [70.9–91.1] vs. 96.4% [89.6–97.8], $P = 0.03$) compared to recipients of grafts from non-DM donors. The adjusted hazard ratio for donor DM on graft survival was 2.21 (1.08–4.53, $P = 0.03$). In conclusion, donor DM is associated with diminished outcome early after liver transplantation. The increased incidence of HAT after transplantation of livers from DM donors requires further research.

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Introduction

The ongoing gap between the supply of and demand for donor livers available for transplantation has led to an increase in the use of extended criteria donor (ECD) livers. Conventional ECD parameters include donors with higher age, abnormal liver function tests, hypernatremia, hepatic steatosis, prolonged intensive care unit stay, use of vasopressors, resuscitation, and donors positive for viral hepatitis B or C. Donation after circulatory death, or donors with comorbidities, such as hypertension or diabetes mellitus (DM) are considered additional risk factors [1].

Globally, the number of people with DM has more than doubled over the past two decades. In the United States, 23.7 million adults were diagnosed with DM in 2011 and this number is expected to increase to 29.6 million in 2030, making up 11.8% of the national population [2]. In the Netherlands, 8.8% of the national population is expected to to be living with DM by 2030 [3]. Consequently, an increasing number of potential deceased organ donors is likely to have DM.

DM is associated with nonalcoholic fatty liver disease (NAFLD) [4], which is a spectrum of diseases ranging from hepatic steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis [5,6]. In addition, DM has been associated with an impaired liver microvascular circulation, making these grafts more vulnerable to ischemic injury sustained during transplantation [7].

Studies on the use of liver grafts derived from donors with DM have not yet been performed in European cohorts, and there are currently no published data on early postoperative complications, such as primary nonfunction (PNF) and hepatic artery thrombosis (HAT) after liver transplantation using grafts from DM donors [8–10]. Also, there are no studies comparing outcome after transplantation of livers from donors with type 1 (DM1) versus type 2 DM (DM2). The pathophysiology of DM1 versus DM2 is different, with the latter being more often associated with the metabolic syndrome and NAFLD [4,11,12]. We, therefore, hypothesized that outcome after transplantation of livers from DM2 donors would be inferior to that of livers from DM1 donors.

We conducted a national multicenter study to examine early postoperative outcome after transplantation with liver grafts from DM donors compared to non-DM donors, and we assessed whether the type of DM influences the outcome.

Patients and methods

Study population

We performed a retrospective cohort study including all consecutive patients who underwent liver transplantation with a graft derived from a donor with DM between January 1, 1996, and December 31, 2016, in the Netherlands. Exclusion criteria included recipient age < 18 years, split liver grafts, and combined organ transplantation. Donor characteristics were obtained from Eurotransplant. A donor was considered to be diabetic when the box "diabetes mellitus" in the Eurotransplant database was ticked "yes," or if it was explicitly stated in the box "other comments." A distinction between DM1 versus DM2 was made based on the specific description "type 1" or "type 2" next to the box "diabetes mellitus" in the Eurotransplant database or in the box "other comments." A graft was considered "steatotic" if the radiology report specifically stated "hepatic steatosis" or if the "steatosis" box in the NTS quality form was ticked "yes." Recipient characteristics and surgical variables were derived from prospectively maintained databases in each participating center. Post-transplantation laboratory data were obtained from chart review. The study was approved by the Institutional Review Board of the University Medical Center Groningen (202000250) and adhered to the Declaration of Helsinki and the Declaration of Istanbul. The study was performed consistent with STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines.

To examine the effect of donor DM on outcome after liver transplantation, all recipients receiving a graft from a DM donor were individually matched at random with two recipients who received a liver from a non-DM donor. To eliminate any confounding by a "center effect," the matching process was stratified per transplant center. Matching was based on the following variables: year of transplantation (±2 years), whether it was a retransplantation, and the balance of risks (BAR) score (±2 points). The BAR score predicts post-transplant survival, and the formula is based on the Model for End-stage Liver Disease (MELD) score, retransplantation, whether the patient was receiving life support prior to the transplantation, recipient age, cold ischemia time (CIT), and donor age [13]. The BAR score was calculated on the day of liver transplantation.

Outcome parameters

Early post-transplant outcome was considered the primary outcome of this study. PNF was defined as non-life-sustaining liver function requiring retransplantation or leading to death within 7 days after transplantation. HAT was defined as a radiologically or surgically proven thrombosis of the hepatic artery. Graft loss was defined as the time between transplantation and death related to graft failure or retransplantation. Patients that died with a functioning graft were censored in the graft survival analysis. Patient survival was defined as the time interval between transplantation and all-cause mortality. Late post-transplant outcome was evaluated as a secondary outcome. Nonanastomotic biliary strictures (NAS) were defined as any stricture of the donor bile duct except those localized near the biliary anastomosis and in the absence of HAT. Outcomes were analyzed by type of donor DM. Follow-up was recorded up to 3 years after baseline, or until December 31, 2017.

Statistical analysis

Categorical variables were presented as numbers and percentages. Continuous variables were presented as median and interquartile range. Comparisons between the groups were made using chi-square test for categorical variables and Mann–Whitney U test for continuous variables. Unadjusted 3-year Kaplan–Meier survival curves were used to graphically depict graft and patient survival stratified by donor DM status, and differences between the groups were evaluated using the log-rank test. Cox proportional-hazards regression modeling was used to assess the effect of donor DM on 3-year graft survival after adjustment for relevant factors selected by backward elimination techniques. The following variables were analyzed in the first step of the backward elimination process after careful selection based on literature and background knowledge [9,10,13,14]: donor DM, recipient age, MELD score, and whether it was a retransplantation. Risk related to graft failure was expressed as hazard ratio (HR) with 95% confidence interval (CI). Analyses by a Cox proportional-hazards model was chosen, because matching was performed by using the entire database of non-DM donors in the Netherlands (n = 2,616) to search, at random, for the nearest (by date of transplantation) potential match by BAR score and retransplantation rendering the risk of within-cluster homogeneity as low.

A P-value of 0.05 or less was considered significant. All analyses were conducted using the statistical software SPSS version 23.0 (SPSS Inc., Chicago, IL, USA).

Results

Donor diabetes

During the study period, 2,351 adult patients received a deceased donor liver, of whom 69 (2.9%) received a graft derived from a donor with DM. The proportion of liver donors with DM has increased over the years (Fig. 1). Recipients of DM donor livers were matched to a control group consisting of 138 recipients of non-DM donor livers, adding up to a total of 207 recipients included in this study. The median follow-up time was 49 (18–71) months in the DM donor group and 43 (24–57) months in the non-DM donor group. Of DM donors, 19 (27.5%) had DM1 and 41 (59.4%) had DM2. Data on type of DM were missing for 9 cases (13.0%). These 9 missing cases were excluded for subanalysis on the influence of type of donor DM.

Donor and recipient characteristics

There were no significant differences between recipients of the study group and the matched control group. DM donors had a slightly higher body mass index (BMI) compared to non-DM donors (26 (24–29) vs. 25 (23–27), $P = 0.02$) and were more likely to suffer from hypertension compared to non-DM donors (58.5% vs. 26.4%, $P < 0.01$) (Table 1). Although DM donors

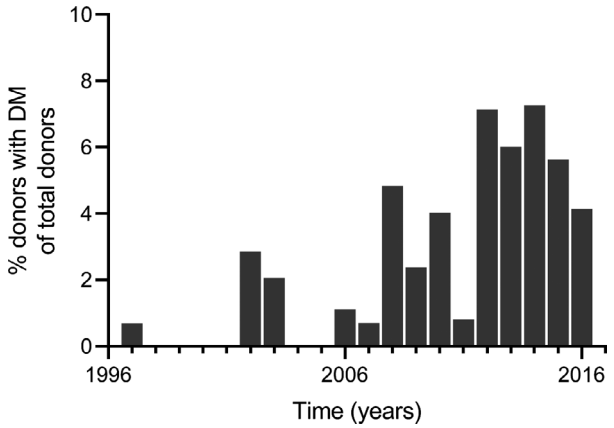

Figure 1 Percentage of donors with diabetes between 1996 and 2016 in the Netherlands. Data on total number of liver donors were obtained from the Dutch Transplant Society [28]. The bars represent the percentage of donors with DM of the total number of liver donors in the corresponding year.

tended to more often die from anoxia (17.4% vs. 8.7%, $P = 0.07$) and to have alcohol abuse (19.6% vs. 9.6%, $P = 0.07$), these differences did not reach statistical significance. The percentage of steatotic grafts was not different between DM versus non-DM donors (19.1% vs. 18.6%, $P = 0.95$), but data were only available for 106/207 donors. Cold and warm ischemia times were not different between the study group and the control group.

Early post-transplant outcomes

PNF was observed in 5.8% of grafts derived from DM donor grafts, compared to 2.9% of non-DM donor grafts ($P = 0.31$) (Table 2). Grafts derived from a donor with a history of DM were significantly more often complicated with HAT after liver transplantation (8.7% vs. 2.2%, $P = 0.03$). Recipients of livers from DM donors had lower 90-day graft (88.4% [70.9–91.1] vs. 96.4% [89.6–97.8], $P = 0.03$) and patient (92.8% [86.9–95.6] vs. 97.1% [93.3–99.3], $P = 0.31$) survival compared to recipients of livers from non-DM donors, but the difference was only significant for graft survival.

Late post-transplant outcomes

The incidence of NAS was nonsignificantly lower in the DM donor group (14.5% vs. 21.4%, $P = 0.26$). Three-year graft (78.3% [66.6–86.3] vs. 89.1% [82.6–93.3], $P = 0.03$) and patient (84.0% [73.0–91.3] vs. 95.7% [90.5–98.0], $P = 0.01$) survival were significantly lower for recipients receiving a liver graft from a DM donor compared to those who received a graft from a non-DM donor (Fig. 2).

Table 1. Recipient, donor, and surgical variables by donor diabetes mellitus status

	Overall ($n = 207$)	Diabetic donor ($n = 69$)	Nondiabetic donor ($n = 138$)	*P*-value*
Recipient variable				
Age (years)	54 (45–60)	54 (45–59)	54 (45–60)	0.89
Female, % (*n*)	32.4% (67)	40.6% (28)	28.3% (39)	0.08
BMI (kg/m^2)	25 (23–29)	25 (23–29)	25 (23–29)	0.51
BAR score	7 (3–12)	7 (3–12)	7 (3–12)	0.70
Laboratory MELD score	18 (12–25)	19 (12–28)	18 (13–25)	0.56
Retransplantation, % (*n*)	17.4% (36)	17.4% (12)	17.4% (24)	>0.99
HCV, % (*n*)	14.5% (30)	15.9% (11)	13.8% (19)	0.68
NASH, % (*n*)	8.7% (18)	8.7% (6)	8.7% (12)	>0.99
Donor variables				
Age (years)	57 (46–64)	59 (49–65)	56 (43–64)	0.08
Female, % (*n*)	42.5% (88)	45.3% (31)	44.0% (61)	0.87
BMI (kg/m^2)	25 (23–28)	26 (24–29)	25 (23–27)	0.02
DCD, % (*n*)	18.4% (38)	15.9% (11)	19.6% (27)	0.53
Cause of donor death, % (*n*)				
CVA	66.7% (138)	62.3% (43)	68.8% (95)	0.33
Trauma	14.5% (30)	13.0% (9)	15.2% (21)	0.65
Anoxia	11.6% (24)	17.4% (12)	8.7% (12)	0.07
Other	7.2% (15)	7.3% (5)	7.3% (10)	0.66
Comorbidities, % (*n*)				
Hypertension	36.8% (76)	58.5% (40)	26.4% (36)	<0.01
Smoking	61.5% (127)	67.8% (47)	58.4% (81)	0.24
Alcohol	12.9% (27)	19.6% (14)	9.6% (13)	0.07
Hepatic steatosis, % (*n*)	18.9% (20#)	19.1% (9#)	18.6% (11)	0.95
Surgical variables				
CIT (min)	402 (340–478)	386 (332–454)	415 (341–483)	0.31
WIT (min)	34 (28–40)	34 (29–43)	35 (28–40)	0.39

BAR, balance of risks; BMI, body mass index; CIT, cold ischemia time; CVA, cerebrovascular accident; DCD, donation after circulatory death; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis; WIT, warm ischemia time. Numbers are expressed as percentages (number) or median (interquartile range).

**P*-value is based on columns diabetic donor versus nondiabetic donor. A *P*-value < 0.05 was considered significant. # there were missing data for this variable.

Table 2. Post-transplant outcomes after liver transplantation with grafts from diabetic versus nondiabetic donors

Variable	Diabetic donor (n = 69)	95% CI	Nondiabetic donor (n = 138)	95% CI	P-value
Early post-transplant outcomes					
PNF	5.8% (4)	1.6–14.2	2.9% (4)	0.8–7.3	0.31
HAT	8.7% (6)	3.3–18.0	2.2% (3)	0.5–6.2	0.03
90-day graft survival	88.4% (61)	70.9–91.1	96.4% (133)	89.6–97.8	0.03
90-day patient survival	92.8% (64)	86.9–95.6	97.1% (134)	93.3–99.3	0.31
Late post-transplant outcomes					
NAS	14.5% (10)	7.2–25.0	21.0% (29)	13.9–30.5	0.26
3-year graft survival	78.3% (54)	66.6–86.3	89.1% (123)	82.6–93.3	0.03
3-year patient survival	84.0% (58)	73.0–91.3	95.7% (133)	90.5–98.0	0.01

CI, confidence interval; HAT, hepatic artery thrombosis; PNF, primary nonfunction; NAS, nonanastomotic biliary strictures. Numbers are expressed as percentages (number). Outcomes were compared using the chi-square test. A P-value < 0.05 was considered significant.

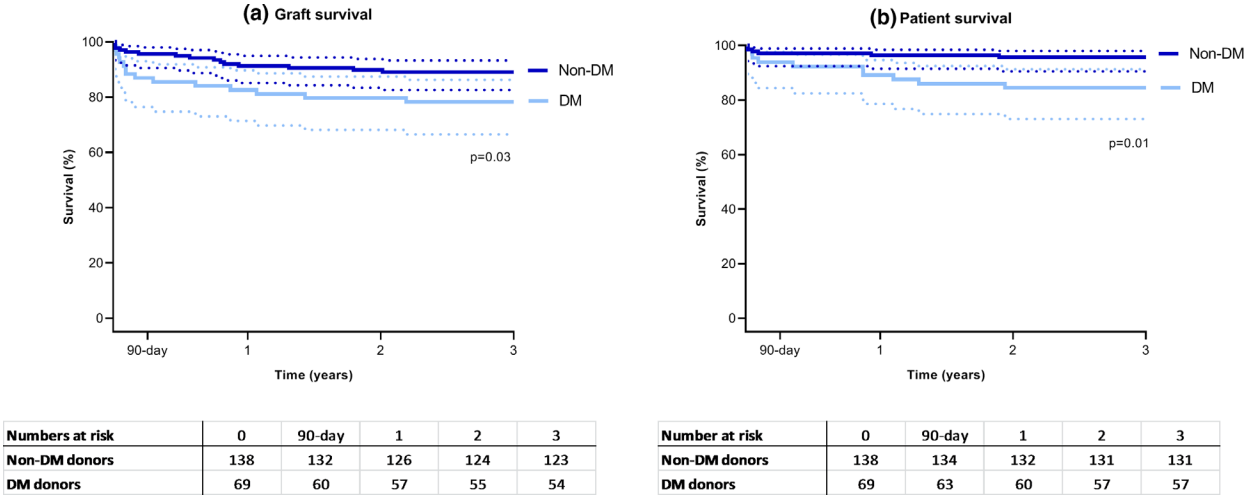

Figure 2 Graft and patient survival after liver transplantation of grafts from nondiabetic donors versus diabetic donors. Unadjusted Kaplan–Meier survival curves are shown for 3-year graft and patient survival. Comparisons between the groups were made using the log-rank test. Dotted line represents 95% confidence interval. Abbreviations: DM, diabetes mellitus.

According to the Cox model, donor DM was associated with a higher 3-year risk of graft loss compared to donors without DM with a HR of 2.15 (1.05–4.40, P = 0.04). After adjusting for the risk factors in multivariable analyses (recipient age, MELD score and retransplantation), donor DM remained associated with a higher risk of graft loss with an adjusted hazard ratio of 2.21 (1.08–4.53, P = 0.03) (Table 3).

Donor diabetes type 1 versus type 2

Donors with DM2 were older (61 (55–67) vs. 49 (43–60), P < 0.01), had a higher BMI (26 (25–29) vs. 24 (22–27), P = 0.04), and had more often died from a cerebrovascular accident (73.2% vs. 36.8%, P = 0.01), compared to DM1 donors. Of the data available, 0/12 (0.0%) grafts were steatotic in the DM1 group, whereas 6/30 (20.0%) grafts from DM2 donors had steatosis (P = 0.09) (Table S1).

There were no significant differences in early post-transplant outcomes between recipients of livers from donors with DM1 versus DM2 (Table 4). Ninety-day graft and patient survival were 84.2% [58.7–94.6] and 94.7% [79.0–97.6] in the DM1 group and 92.7% [68.1–99.2] and 92.7% [79.0–97.6] in the DM2 group, respectively. The incidence of NAS was almost two times higher in livers from DM1 donors, compared to DM2 donors, but this difference did not reach statistical significance

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Table 3. Multivariable Cox proportional-hazards regression model for graft survival after liver transplantation

Variable	HR	95% CI	*P*-value
Recipient			
Age	0.96	0.94–0.99	<0.01
Donor			
Diabetes	2.21	1.08–4.53	0.03

CI, confidence interval; HR, hazard ratio; MELD, model for end-stage liver disease.

Graft survival was defined as death-censored graft failure or retransplantation. The multivariable model was conducted via a backwards stepwise approach. The following variables were analyzed in the first step of the multivariable model: donor diabetes, recipient age, recipient MELD score, and whether it was a retransplantation. A *P*-value < 0.05 was considered significant.

(21.1% vs. 12.2%, $P = 0.37$). Three-year graft and patient survival were 78.9% [53.2–91.5] and 84.2% [62.1–87.9] in the DM1 group and 78.0% [58.7–94.6] and 87.5% [72.5–94.6] in the DM2 group, respectively.

Discussion

The growing incidence of DM is a worldwide phenomenon, and it is therefore not unlikely that the number of organ donors with a history of DM will increase in the near future. In this national multicenter study, we found inferior early post-transplant outcomes for recipients of liver grafts from DM donors compared to non-DM donors.

Several studies have reported on outcomes associated with recipient DM at the time of liver transplantation, and it was generally found that recipient DM is associated with inferior outcome [15–18]. Only few studies analyzed the effect of donor DM on outcome following liver transplantation [8–10]. In accordance with previous studies, we found reduced graft and patient survival for recipients of livers from DM donors, compared to non-DM donors [9,10]. It is worth mentioning that there are notable differences in donor characteristics between our study performed in a European cohort versus previous studies in American cohorts [9,10]. For example, the DM donors in this study had a lower BMI (26 versus 30) and less often suffered from additional hypertension (60% vs. 75–80%) compared to DM donors in studies using American data registries [8,9].

As a novel finding, this study showed a higher incidence of HAT after transplantation using livers from donors with DM. In the literature, DM has been associated with an impaired liver microvascular circulation, making these grafts more vulnerable to ischemic injury, and potentially increasing the risk of vascular complications after liver transplantation [7,19,20]. Previous reports on liver transplant recipients with DM have suggested an increased prevalence of vascular complications after transplantation [21,22]. Also, higher rates of late onset HAT have been described in transplant recipients with new-onset DM after transplantation [23]. As suggested by Fiel et al., identification of histological markers of DM-related liver injury, such as vascular wall

Table 4. Post-transplant outcomes after liver transplantation with grafts from donors with diabetes type 1 versus type 2

Variable	Donor DM type 1 (*n* = 19)	95% CI	Donor DM type 2 (*n* = 41)	95% CI	*P*-value
Early post-transplant outcomes					
PNF	5.2% (1)	0.1–26.0	4.9% (2)	0.6–16.5	0.94
HAT	10.5% (2)	1.3–33.1	9.8% (4)	2.7–23.1	0.57
90-day graft survival	84.2% (16)	58.7–94.6	92.7% (38)	68.1–99.2	0.31
90-day patient survival	94.7% (18)	79.0–97.6	92.7% (38)	79.0–97.6	0.77
Late post-transplant outcomes					
NAS	21.1% (4)	6.1–45.6	12.2% (5)	4.1–26.2	0.37
3-year graft survival	78.9% (15)	53.2–91.5	78.0% (32)	58.7–94.6	0.94
3-year patient survival	84.2 (16)	62.1–87.9	87.5 (35)	72.5–94.6	0.73

CI, confidence interval; DM, diabetes mellitus; HAT, hepatic artery thrombosis; PNF, primary nonfunction; NAS, nonanastomotic biliary strictures.

Numbers are expressed as percentages (number). Outcomes were compared using the chi-square test. A *P*-value < 0.05 was considered significant.

thickness, and their correlation with worse outcome after transplantation could be of interest for future research [24]. If larger cohort studies confirm an increased risk of vascular complications in DM donor grafts, more targeted therapy or diagnostics may be used to prevent thrombosis in these livers. Graft steatosis may have an impact on outcome after transplantation using grafts from DM donors. Unfortunately, a high number of missing data hampered thorough analysis on the influence of donor graft steatosis. Of the data available, the percentage of grafts with steatosis among DM versus non-DM donors was similar. Moreover, DM donors only had a slightly higher BMI, which has previously been used as a surrogate marker for hepatic steatosis by others [10,25,26]. We, therefore, suggest that microvascular changes in DM donor grafts rather than the amount of steatosis contribute to diminished outcome after transplantation, but this remains speculative.

To the best of our knowledge, this is the first study describing the effect of type 1 versus type 2 donor DM. The incidence of NAS was almost two times higher in livers from DM1 donors, compared to DM2 donors, but these differences did not reach statistical significance. Yet, this study was not powered to detect differences between type of donor DM and confirmation of these observations should follow from studies in larger cohorts. Noteworthy, DM2 has an etiological role in NAFLD, which could progress to cirrhosis and hepatocellular carcinoma [27], but donor livers with signs of fibrosis or cirrhosis will not be accepted for transplantation suggesting that only selected DM2 livers were included in this study.

Although the present study provides new information on the impact of donor DM on liver transplantation outcomes, it has some limitations, such as the relatively small sample size. As such, we were only able to analyze a small number of variables in our multivariable model. We acknowledge that the influence of donor graft steatosis, the duration of donor DM, and type of DM medication can be of interest, but these variables could not be analyzed as they are scarcely reported in the Eurotransplant donor database. The influence of incomplete data and the accuracy of the data registry are recurrent limitations of registry database studies, carrying an inherent bias.

In conclusion, donor DM is a risk factor for diminished outcome in the early postoperative period after liver transplantation. The increased incidence of HAT after transplantation of livers from DM donors requires further research.

Authorship

IMAB: designed the study, collected and analyzed data, and wrote the paper; MR: collected and analyzed data, and revised the paper; IV: collected data and revised the paper; DH: curated data and revised the paper; BH: curated data and revised the paper; AFS: curated data and revised the paper; IPJA: curated data and revised the paper; APB: curated data and revised the paper; VEM: curated data and revised the paper; SDM: curated data and revised the paper; WGP: designed the study, curated data, interpreted results, and revised the manuscript; RJP: designed the data, curated data, interpreted results, and revised the manuscript.

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Conflicts of interest

The authors have declared no conflicts of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Recipient, donor, and surgical variables by type of donor diabetes mellitus.

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