Ongoing Donor-transmitted Diabetic Kidney Disease in Kidney Transplant Recipients with Fair Sugar Control: a single center retrospective study

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Abstract

Background Transplantation with a diabetic donor kidney may have some benefits compared to remaining on the waitlist for selected patients. However, we found that some kidney transplant recipients have ongoing donor-transmitted diabetic kidney disease (DT-DKD) despite fair blood sugar control. This study aimed to survey the incidence and clinical pattern of DT-DKD in kidney transplant recipients.

Methods We retrospectively reviewed the medical records of kidney transplantations in our hospital. We found 357 kidney transplantations from February 2006 to April 2018. Among these, 23 (6.4%) diabetic donor kidney transplantations were done in the study period.

Results Among the 23 recipients, 6 (26.1%) displayed biopsy-proven DKD. Recipients with biopsy-proven DKD had longer dialysis vintage, higher proteinuria amount, lower last estimated glomerular filtration rate (eGFR), and a more rapid decline in the eGFR. The median fasting blood sugar level in the biopsy-proven DKD group was unexpectedly lower than the non-DKD group. Most of the pre-implantation frozen sections in biopsy-proven DKD group showed diabetic lesions worse than diabetic nephropathy (DN) class IIa. In the biopsy-proven DKD group, 5 recipients had no history of diabetes before or after transplantation. Among the 23 recipients, 5 (21.7%) were diagnosed with DT-DKD. Serial post-transplant biopsies showed the histological progression of allograft DN.

Conclusions To the best of our knowledge, this is the first study to report the phenomenon of ongoing DT-DKD in kidney transplant recipients with fair blood sugar control. The zero-time pre-transplant kidney biopsy may be an important examination before the allocation of diabetic donor kidneys.

Background

According a report by the United States Renal Data System, the incidence and prevalence of end-stage renal disease (ESRD) in Taiwan has persistently been one of the highest worldwide [1]; this has led to serious medical and socioeconomic problems in the country [2]. According to the statistical data of the Taiwan Organ Registry and Sharing Center, more than 7,400 ESRD patients were waitlisted for kidney transplantation in 2018. However, only 317 kidney transplantations (including 151 deceased donor and 166 living donor kidney transplantations) were performed in 2018 [3]. The appropriate utilization of marginal or extended criteria donors is one of the possible solutions to the organ shortage crisis [4–5]. Few studies have surveyed the impact of diabetes on the allocation of diabetic donor kidneys against the backdrop of the organ shortage situation. Compared to remaining on the waitlist or receiving a kidney from a non-diabetic extended criteria donor, transplantation with a diabetic donor kidney may have benefits for selected patients [6–9]. Some studies have shown the improvement of early diabetic lesion in the transplanted kidney if the recipient has good post-transplant glycemic control [10–11]. However, we found that some kidney transplant recipients have biopsy-proven ongoing diabetic kidney disease (DKD) despite clinical euglycemia and no history of diabetes. We defined this phenomenon as donor-transmitted

DKD (DT-DKD). The aim of this study was to survey the incidence and clinical pattern of DT-DKD in kidney transplant recipients.

Methods

Study design and subjects

We conducted a retrospective cohort study and reviewed the medical record of kidney transplantations at our centre between February 2006 and April 2018. A total of 357 kidney transplantations were performed in the study period. Among these, 23 (6.4%) diabetic donor kidney transplant recipients were included for data analysis (Figure 1). Our study was approved by the institutional review board of Taichung Veterans General Hospital (IRB TCVGH No: CE20012B). Patient informed consent was waived due to the retrospective data analysis nature of this study.

Indication biopsies were done when there was an unexplained increase in serum creatinine or proteinuria. During the study period, 21 of the 23 diabetic donor kidney transplant recipients were found to have undergone at least one post-transplant allograft biopsy. Based on the clinical data and histopathologic results, the 23 diabetic donor kidney transplant recipients were divided into two groups: the biopsy-proven DKD group (n=6) and non-DKD group (no biopsy-proven DKD or no clinical suspicion of DKD; n=17). One recipient in the biopsy-proven DKD group had a history of diabetes before transplantation, and 4 in the non-DKD group had history of diabetes before transplantation. In the non-DKD group, 2 recipients were found to have post-transplant diabetes mellitus (PTDM). All the results of glycated hemoglobin (HbA1c) beyond 3 months post-transplantation were included to calculate the HbA1c after transplantation. Besides, the fasting blood sugar levels after transplantation of all 23 recipients were included to draw the box and whisker plot for evaluating the blood sugar level distribution. The estimated glomerular filtration rate (eGFR) was calculated via the Modification of Diet in Renal Disease Study equation [12].

Statistical analysis

Data are shown as the mean ± standard deviation or median (first quartile, third quartile) for continuous variables according to their distribution, and as number (percentage) for categorical variables. The assessment of normality was conducted using the Kolmogorov-Smirnov test and Shapiro-Wilk test. Statistical analyses were performed using MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium). Tests for statistical significance were conducted using the Mann-Whitney U test for continuous variables, and the Fisher's exact test or Chi-Squared Test for categorical variables. A p value <0.05 was considered statistically significant.

Results

There were 9 male and 14 female diabetic donor kidney transplant recipients with a median age of 44.2 years. The median follow-up duration was 4.4 years. The median baseline estimated glomerular

filtration rate (eGFR) after kidney transplantation was 62.7 ml/min/1.73 m^2, while the last eGFR was 37.7 ml/min/1.73 m^2.

At last follow-up, 6 (26.1%) of the 23 recipients displayed biopsy-proven DKD in the transplanted kidneys. Based on the clinical data and histopathologic results, the selected recipients were divided into two groups: the biopsy-proven DKD group (n = 6) and non-DKD group (n = 17). Table 1 shows the clinical characteristics and comparison of the two groups. Compared with the non-DKD group, the recipients with biopsy-proven DKD group had a longer dialysis vintage (5.9 vs. 2.8 years; p = 0.005), higher proteinuria amount (7.3 vs. 0.2 mg/mg; p = 0.001), lower last eGFR (10.4 vs. 47.3 ml/min/1.73 m^2; p = 0.003), and a more rapid decline in the eGFR (10.6 vs. 5.8 ml/min/1.73 m^2/year; p = 0.017). Zero-time pre-transplant kidney biopsies were done in 11(47.8%) of the 23 kidney transplantations. Pre-implantation frozen sections were available in 4 and 7 cases in the biopsy-proven DKD group and the non-DKD group, respectively. All the 4 frozen sections in the biopsy-proven DKD group showed diabetic lesions worse than diabetic nephropathy (DN) class IIa lesion (class IIa, IIb, IIb, IIb, respectively), as defined by the Renal Pathology Society[13]. However, none of the 7 frozen sections in the non-DKD group displayed DN lesion worse than DN class IIa (p = 0.003). One graft failure due to DKD was noted in the biopsy-proven DKD group.

Figure 2 presents the fasting blood sugar level distribution of the 23 diabetic donor kidney transplant recipients. The median fasting blood sugar level in the biopsy-proven DKD group was unexpectedly lower than those in the non-DKD group (90 vs. 96 mg/dl; p < 0.0001; Fig. 2A). Subgroup analyses show that the median fasting blood sugar level in the biopsy-proven DKD group was higher among the recipients with diabetes (159 vs. 121 mg/dl; p < 0.0001; Fig. 2B), and lower among the recipients without diabetes (86.5 vs. 89 mg/dl; p < 0.0001; Fig. 2C).

In the biopsy-proven DKD group, 5 recipients had no history of diabetes before or after transplantation. Hence, 5 (21.7%) of the 23 recipients were diagnosed with DT-DKD. Table 2 shows the clinical characteristics of the 5 recipients with DT-DKD. Serial post-transplant biopsies showed the progression of allograft diabetic lesion.

Discussion

To the best of our knowledge, this is the first study to report the phenomenon of ongoing DT-DKD in non-diabetic kidney transplant recipients with fair blood sugar control. Few studies have previously evaluated the reversal of DN after transplantation into non-diabetic recipients. Abouna et al. [10] reported a deceased donor with a 17-year history of type 1 diabetes. Pre-transplant histological examination showed features of DN including thickening of basement membranes and diffuse glomerulosclerosis. After transplantation into two non-diabetic recipients, reversal of DN was found at 7 months post-transplantation in both transplant kidneys. Harada et al. [11] also reported the reversal of early stage DN in grafts from three living diabetic donors after transplantation into non-diabetic recipients. In our study, 11 of 23 kidney transplantations had undergone pre-transplant histological examinations. 7 pre-

implantation frozen sections showed no obvious DN. However, we cannot rule out the possible RPS class I DN in these transplant kidneys because some class I DN kidneys showed glomerular basement membranes thickening only when examined using electron microscopy. Therefore, we cannot exclude the possible reversal of early stage DN in some recipients of our cohort.

Recently, Truong et al. [14] reported 26 diabetic donor kidney transplantations with post-perfusion biopsies and follow-up biopsies. Among their study subjects, 2 transplanted kidneys with class IIa DN progressed slowly (class IIa to IIb), but this progress was related to recipient diabetes in both cases. They also reported that one transplanted kidney without DN before transplantation developed class IIa DN in a recipient with PTDM. In our study, 4 pre-implantation frozen sections in the biopsy-proven DKD group showed diabetic lesions worse than DN class IIa. Besides, all post-transplant allograft biopsies of the 6 recipients in our biopsy-proven DKD group showed progression of DN. Our study showed that some transplanted kidneys with later stages of DN may worsen after transplantation into non-diabetic recipients, even if the recipients are non-diabetic and with fair post-transplant blood sugar control. Okada et al. [15] reported early graft loss (16 months and 20 months after transplantation) in two non-diabetic recipients of mate-kidneys from the same diabetic donor. Pre-transplant biopsy in their study showed DN with nodular sclerosis (class III DN). Hence, zero-time biopsy may be an important examination to precisely evaluate the status of DN before allocation of diabetic donor kidneys.

In our study, the median fasting blood sugar level in the biopsy-proven DKD group was unexpectedly lower than in the non-DKD group. This may be related to the poorer renal function in the DKD group. Chronic kidney disease (CKD) is a risk factor for low blood sugar level in patients with or without diabetes [16]. There are many possible mechanisms to explain the association between CKD and low blood sugar level, such as decreased insulin renal clearance, impaired renal gluconeogenesis, diminished insulin degradation, and poor nutrition. Patients with CKD and diabetes are at risk for both hypoglycemia and hyperglycemia [17]. Subgroup analyses in our study showed that the median fasting blood sugar level in the biopsy-proven DKD group was higher among the recipients with diabetes. Chronic inflammation-related insulin resistance as well as decreased glucose filtration and excretion are the possible reasons for hyperglycemic episodes.

Some limitations of this study should be acknowledged. The nature of retrospective study may have some unrecognized confounding factors to bias the findings. Besides, the case number in this study is small. Nevertheless, this study represents real-world conditions. Diabetic donor kidneys account for 6.4% of kidney transplantations in our hospital. This frequency is similar to that reported in studies (3.5%, 6.4%, 5.6%, and 6.1%) by Ahmad, Mohan, Cohen, and Truong, respectively [7–9, 14]. One graft failure, higher proteinuria amount, a more rapid decline in the eGFR, and ongoing DKD were noted in the biopsy-proven DKD group in our study. A previous study showed that diabetic donor kidneys with DN may have little adverse effect on graft survival, and DN may progress slowly or may stabilise[14]. Our findings differ from those of this study, as poorer renal outcomes were noted in recipients with DT-DKD.

Conclusions

To the best of our knowledge, this is the first study to report the phenomenon of ongoing DT-DKD in kidney transplant recipients with fair blood sugar control. Our study showed poorer renal outcomes in these recipients. The zero-time pre-transplant kidney biopsy may be an important examination before the allocation of diabetic donor kidneys. Further study is needed to elucidate the possible mechanism of ongoing DT-DKD in non-diabetic recipients with fair blood sugar control.

Abbreviations

DT-DKD
Donor-transmitted diabetic kidney disease;
eGFR
Estimated glomerular filtration rate
DN
Diabetic nephropathy
ESRD
End-stage renal disease
PTDM
Post-transplant diabetes mellitus
HbA1c
Glycated hemoglobin
CKD
Chronic kidney disease

Declarations

Ethics declarations

Ethics approval and consent to participate

The study and protocol were reviewed and approved by the Medical Ethics Committee of Taichung Veterans General Hospital, IRB No: CE20012B. Written informed consent for participation was waived because of the retrospective nature of the study. The study complies with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The author declare that they have no competing interests.

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Availability of data and materials.

The individual patient-level data was not made publically available due to containing potentially identifying patient data; however, the study data may be made available from the authors upon reasonable request.

Authors' contributions

HFC: drafted the manuscript and involved with data analysis and interpretation.

MCW: pathological diagnosis of graft biopsy, revision of the manuscript.

HFC, SFT, TMY, CKY, MJW, and CHC: revised the manuscript and involved with patient care.

CHC (corresponding author): final approval of the manuscript.

All authors read and approved the final manuscript.

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Tables

characteristics of the 23 diabetic donor kidney transplant recipients

	Recipients with biopsy-proven DKD (n=6)		Recipients without DKD (n=17)		p value
teristics					
	4	(66.7%)	5	(29.4%)	0.162
years ‡	42.5	(32.8-44.2)	46.7	(36.5-52)	0.327
dialysis†	6	(100%)	13	(76.5%)	0.539
on dialysis ‡	5.9	(3.7-9.2)	2.8	(1.8-4.5)	**0.005****
D§					0.854
	1	(16.7%)	4	(23.5%)	1.000
disease†	2	(33.3%)	7	(41.2%)	1.000
	1	(16.7%)	1	(5.9%)	0.462
	2	(33.3%)	5	(29.4%)	1.000
nass index (kg/m^2) ‡	24.8	(21.6-26.7)	21.7	(20.0-25.2)	0.183
recipient†	0	(0%)	2	(11.8%)	1.000
t diabetes mellitus†	0	(0%)	2	(11.8%)	1.000
transplantation (%) ‡	5.4	(5.2-5.5)	5.4	(5.0-6.1)	0.889
ransplantation (%) ‡	5.9	(5.7-5.9)	6.0	(5.5-6.9)	0.674
er transplantation (mg/mg)	7.3	(2.0-10.0)	0.2	(0.1-0.7)	**0.001****
er transplantation (ml/min/1.73m^2) ‡	49.0	(42.2-85.1)	62.9	(53.3-81.2)	0.294
er transplantation (ml/min/1.73m^2) ‡	10.4	(8.9-14.2)	47.3	(32.3-55.2)	**0.003****
rate (ml/min/1.73m^2/year)	10.6	(8.7-14.9)	5.8	(2.6-9.8)	**0.017***
on of follow-up in years	4.2	(3.7-7.3)	5.6	(2.7-10.5)	0.575
	1	(16.7%)	0	(0%)	0.261
stics					
age in years ‡	50.5	(39.0-57.0)	54.0	(37.5-60.0)	0.529
efore transplantation (%)	7.1	(7.0-8.1)	6.7	(6.3-7.1)	0.069
donor†	0	(0%)	2	(11.8%)	1.000
kidney RPS DN classification≧IIa †	4/4[a]	(100%)	0/7[b]	(14.3%)	**0.003***
cteristics					
	1	(16.7%)	6	(35.3%)	0.621
atch†	5	(83.3%)	16	(94.1%)	0.462
function†	3	(50.0%)	3	(17.6%)	0.279
n within 1 year†	2	(33.3%)	4	(23.5%)	0.632
MMF/MPA + steroid maintenance†	5	(83.3%)	13	(76.5%)	1.000
+ MMF/MPA + steroid maintenance†	1	(16.7%)	4	(23.5%)	1.000
	1	(16.7%)	1	(5.9%)	0.462
ing induction†	2	(33.3%)	6	(35.3%)	1.000
epleting induction†	3	(50.0%)	10	(58.8%)	1.000

nsplantations have pre-implantation frozen sections in the biopsy-proven DKD group

ansplantations have pre-implantation frozen sections in the non-DKD group

0.01. †Fisher's exact test. ‡Mann–Whitney U-test. §Chi-Squared Test. Values are expressed as Number (percentage) or Median nge). DT-DKD, donor-transmitted diabetic kidney disease; ESRD, end-stage renal disease; HCV, hepatitis C virus; HbA1c, Glycated CR, urine protein-to-creatinine ratio; eGFR, estimated glomerular filtration rate; RPS DN class, Renal Pathology Society classification of athy; PRA, panel-reactive antibody; HLA, human leukocyte antigen; MMF, Mycophenolate mofetil; MPA, Mycophenolic acid.

characteristics of 5 recipients with ongoing donor-transmitted diabetic kidney disease

	1	2	3	4	5
teristics					
	Female	Male	Male	Male	Female
	32.8	44.2	52.7	27.5	43.6
: dialysis	HD	HD	HD	HD	HD
sis	11.4	6.8	3.7	3.7	5.0
D	GN	Unknown	Analgesic	SLE	Unknown
dex (kg/m^2)	25.9	26.7	23.7	28.0	20.0
recipient	N	N	N	N	N
ıt diabetes mellitus	N	N	N	N	N
transplantation (%)	5.3	5.2	5.5	5.2	5.4
ransplantation (%)	5.3	5.8	5.7	5.9	5.9
:er transplantation (mg/mg)	11.626	5.379	1.980	0.849	10.03
er transplantation (ml/min/1.73m^2)	40.33	57.79	42.16	143.78	44.30
er transplantation (ml/min/1.73m^2)	14.16	11.51	9.28	39.71	5.4
rate (ml/min/1.73m^2/year)	8.72	6.77	10.86	14.87	10.30
low-up in years	3.7	7.4	3.2	7.5	4.0
sy RPS DN classification	IIa→IIb→III†	III	III	IIb→III†	IIb→III→IV†
	N	N	N	N	Y
stics					
ears	39	57	57	22	44
efore transplantation (%)	8.0	7.0	7.0	7.1	6.3
donor	N	N	N	N	N
)sy RPS DN classification	IIa	IIb	IIb	-	-
cteristics					
	N	N	N	N	Y
ıatch	Y	Y	Y	N	Y
function	Y	N	N	N	Y
n within 1 year	Y	N	N	N	Y
MMF/MPA + steroid maintenance	Y	Y	Y	Y	Y
	N	N	N	Y	N
:ing induction	Y	N	N	N	N
epleting induction	N	Y	Y	N	Y

splant biopsies showed the progression of allograft diabetic lesion. Y, yes; N, no; -, not performed; HD, hemodialysis, ESRD, end-stage renal nerulonephritis; SLE, systemic lupus erythematosus; HCV, hepatitis C virus; HbA1c, Glycated hemoglobin; UPCR, urine protein-to-eGFR, estimated glomerular filtration rate; RPS DN classification, Renal Pathology Society classification of diabetic nephropathy; PRA, panel-r; HLA, human leukocyte antigen; MMF, Mycophenolate mofetil; MPA, Mycophenolic acid.

Figures

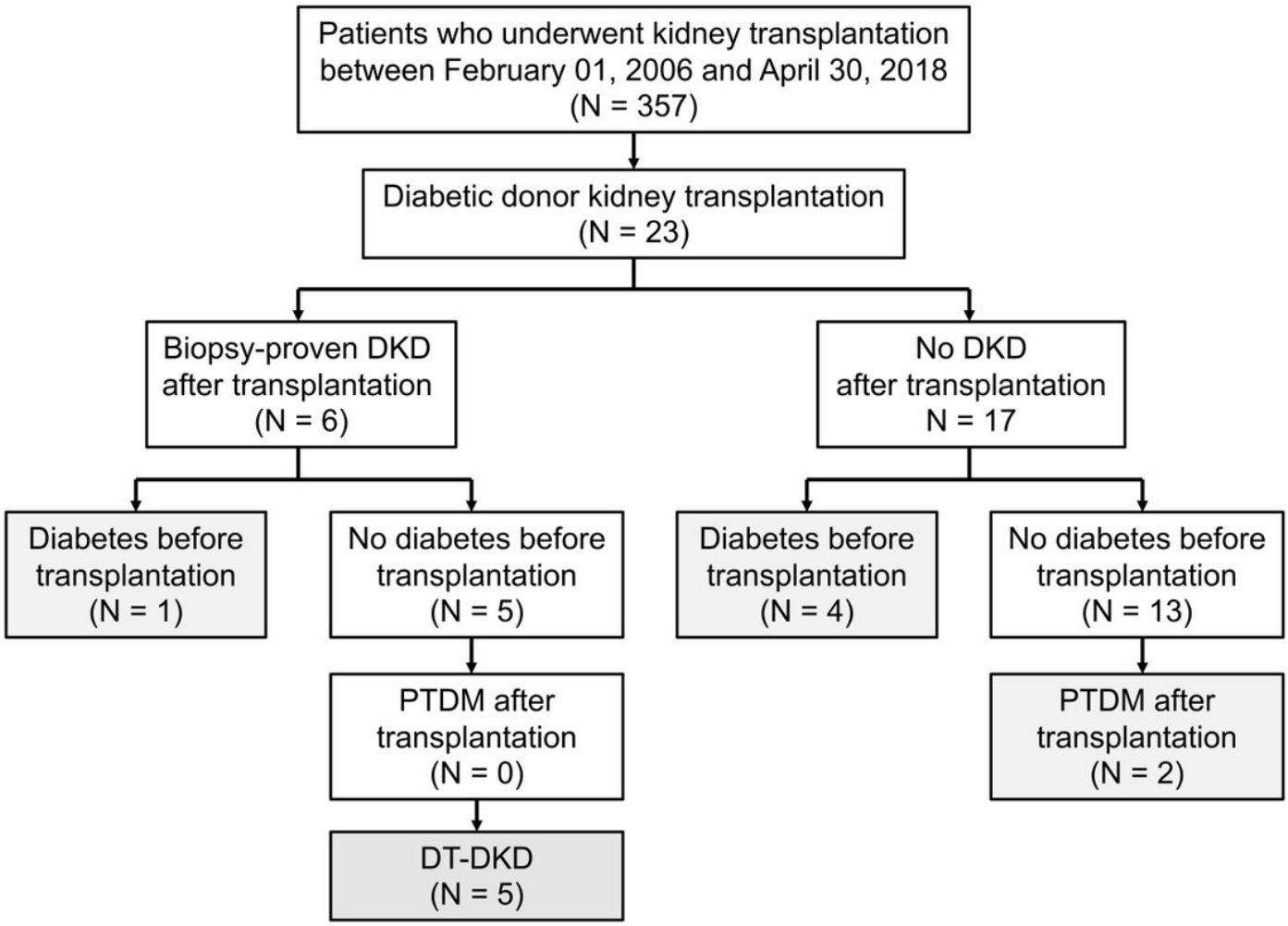

Figure 1

Flow diagram of the study patients. DT-DKD, donor-transmitted diabetic kidney disease; PTDM, post-transplant diabetes mellitus.

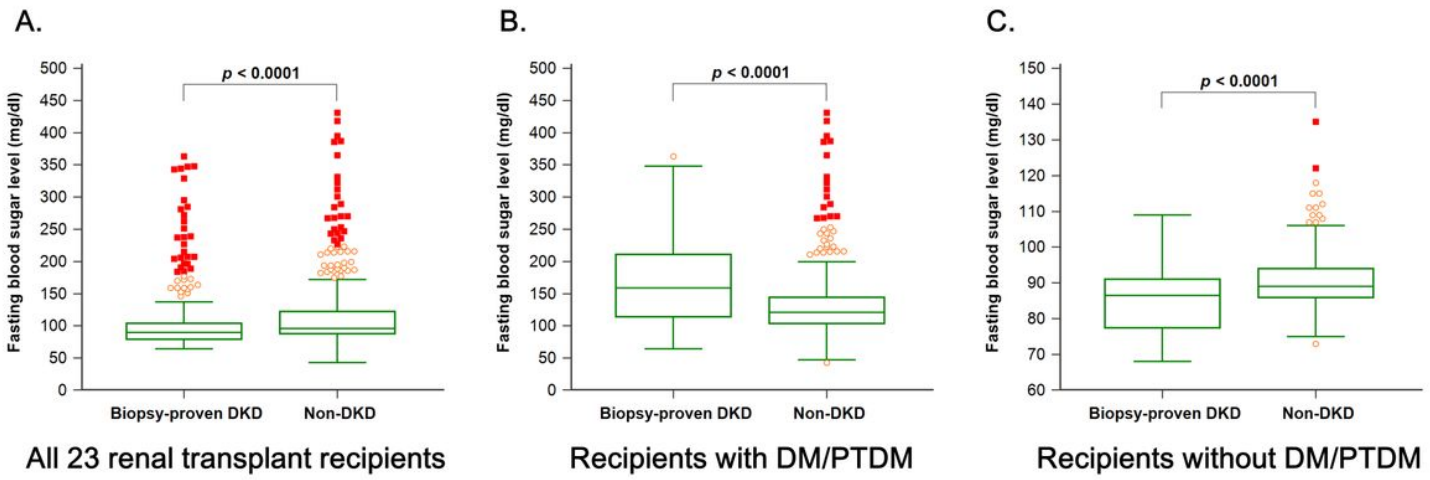

Figure 2

A. The fasting blood sugar level distribution of the 23 diabetic donor kidney transplant recipients. B. The fasting blood sugar level distribution of the recipients with diabetes. C. The fasting blood sugar level distribution of the recipients without diabetes. PTDM, post-transplant diabetes mellitus.