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Post-transplant Diabetes Mellitus in Kidney Transplant Recipients: A Multicenter Study

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Key Points

- Post-transplant diabetes mellitus (PTDM) occurred commonly in a multicenter longitudinal cohort of 632 kidney transplant recipients.
- Independent risk factors for PTDM included older recipient age and higher body mass index at time of transplant.
- PTDM was not associated with adverse graft outcomes or mortality at a median follow-up of 6 years after transplant.

Abstract

Background *De novo* post-transplant diabetes mellitus (PTDM) is a common complication after kidney transplant (KT). Most recent studies are single center with various approaches to outcome ascertainment.

Methods In a multicenter longitudinal cohort of 632 nondiabetic adult kidney recipients transplanted in 2010–2013, we ascertained outcomes through detailed chart review at 13 centers. We hypothesized that donor characteristics, such as sex, HCV infection, and kidney donor profile index (KDPI), and recipient characteristics, such as age, race, BMI, and increased HLA mismatches, would affect the development of PTDM among KT recipients. We defined PTDM as hemoglobin A1c ≥6.5%, pharmacological treatment for diabetes, or documentation of diabetes in electronic medical records. We assessed PTDM risk factors and evaluated for an independent time-updated association between PTDM and graft failure using regression.

Results Mean recipient age was 52±14 years, 59% were male, 49% were Black. Cumulative PTDM incidence 5 years post-KT was 29% (186). Independent baseline PTDM risk factors included older recipient age ($P<0.001$) and higher BMI ($P=0.006$). PTDM was not associated with all-cause graft failure (adjusted hazard ratio (aHR), 1.10; 95% CI, 0.78 to 1.55), death-censored graft failure (aHR, 0.85; 95% CI, 0.53 to 1.37), or death (aHR, 1.31; 95% CI, 0.84 to 2.05) at median follow-up of 6 (interquartile range, 4.0–6.9) years post-KT. Induction and maintenance immunosuppression were not different between patients who did and did not develop PTDM.

Conclusions PTDM occurred commonly, and higher baseline BMI was associated with PTDM. PTDM was not associated with graft failure or mortality during the 6-year follow-up, perhaps due to the short follow-up time.

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Introduction

Although kidney transplant (KT) survival has improved over the last decade, complications arising after KT may affect recipients' long-term health and quality of life. Post-transplant diabetes mellitus (PTDM) is a common metabolic complication experienced by KT recipients (1). The risk of developing PTDM is highest within the first year after KT, and has been linked to poor graft and patient survival (1–6). PTDM also incurs a heavy cost for Medicare; it is estimated that for each KT recipient newly diagnosed with diabetes within 2 years of KT, Medicare pays an additional US$21,500 (7).

Multiple risk factors for *de novo* PTDM have been reported. Some potentially modifiable risk factors include higher body mass index (BMI), weight gain after transplant, hepatitis C virus (HCV) infection, immunosuppressive medications (mainly prednisone and tacrolimus), hypomagnesemia, decreased physical activity, and unhealthy diet (high in fat and cholesterol) (1,3,4,8–16). In contrast, some nonmodifiable risk factors for PTDM include recipient genetic polymorphisms, older age at time of transplant, Black race, history of prior transplantation, male donor status, deceased-donor KT, and increased HLA mismatches (1,3,4,8–16). Many risk factors for PTDM are the same as those for type 2 DM, with additional transplant-specific factors such as immunosuppression and HCV (17). Identification of risk factors, especially modifiable ones, allows for robust pretransplant assessment and preparation for KT in an effort to reduce the risk of PTDM. According to data from the United States Renal Data System, KT recipients who developed PTDM were at a higher risk for death-censored graft failure (dcGF) and death, compared with KT recipients who did not develop PTDM (4). Other published findings similarly suggest that PTDM reduces the lifetime of the graft and contributes to premature mortality in KT recipients (1–3,5,6).

Prior studies report a wide range of PTDM incidence, from 2% to 50% (1). This variability arises from differences in diagnostic criteria and length of follow-up. The 2003 International Consensus Guidelines defined PTDM by the presence of at least one of the following: diabetic symptoms (polyuria, polydipsia, or unexplained weight loss) and plasma glucose concentrations ≥200 mg/dl (11.1 mm), fasting plasma glucose ≥126 mg/dl (7.0 mm), or 2-hour plasma glucose ≥200 mg/dl (11.1 mm) during an oral glucose tolerance test (18). In 2011, the American Diabetes Association (ADA) added a criterion for diabetes diagnosis: hemoglobin A1c ≥6.5% (19). Definitions used to diagnose PTDM in prior literature (2009–2019) are summarized in Supplemental Table 1. Length of follow-up is imperative in the assessment of PTDM because transient hyperglycemia, which may be variably diagnosed as PTDM, commonly occurs in the period immediately after KT due to immunosuppressive medications, stress from surgery, and transplant-related infections (20,21).

Due to changes in immunosuppression and kidney allocation, the expansion of KT donor and recipient pools by accepting more donors and recipients at elevated risk for adverse transplant outcomes, and lack of robust multicenter analyses of PTDM, we aimed to reassess risk factors and occurrence of PTDM among KT recipients in a longitudinal multicenter cohort. We hypothesized that donor characteristics such as sex, HCV infection, and kidney donor profile index (KDPI) and recipient characteristics such as age, race, BMI, and increased HLA mismatches would affect the development of PTDM among KT recipients. We identified PTDM development using multiple sources, such as laboratory values, pharmacological treatment for diabetes, and clinical diagnosis in electronic medical records. In a multicenter cohort of adult KT recipients of deceased-donor kidneys from 13 US transplant centers, we studied baseline and post-KT risk factors for PTDM, and the association between PTDM and adverse graft outcomes.

Methods

Study Cohort Generation and Data Source

This is an ancillary study to the Deceased Donor Study (DDS), an ongoing multicenter, observational, cohort study of deceased donors and their kidney recipients. The DDS study population and methods has been described in detail elsewhere (22–25). Briefly, five organ procurement organizations (OPOs) enrolled donors between May 2010 and December 2013 and followed their own protocols for research authorization and donor management. Clinical variables were abstracted from OPO donor charts. Recipients of these kidneys were identified at 13 participating transplant centers where detailed chart review was performed. All exposures and outcomes were assessed by usual care practices. Trained site coordinators reviewed medical records and recorded detailed recipient characteristics, treatments, and outcomes. Study staff at the data coordinating center validated abstracted data to confirm data quality and accuracy (Supplemental Appendix A). In addition, data for all kidney recipients and donors were obtained from the Organ Procurement and Transplantation Network (OPTN). We excluded recipients on the basis of the following criteria: age <16 years, without any follow-up data, *en bloc* transplant, or multiorgan transplants. We also excluded recipients with known history of pretransplant diabetes, defined as need for insulin or oral hypoglycemic medications at time of transplant, including patients with DM as the cause of ESKD.

The OPTN data system includes data on all donors, waitlisted candidates, and transplant recipients in the United States, submitted by the members of the OPTN, and is described more fully elsewhere (26). The Health Resources and Services Administration, US Department of Health and Human Services provides oversight of the activities of the OPTN. These analyses are on the basis of OPTN data provided by the United Network for Organ Sharing (UNOS) as of December 2018. The OPO scientific review committees and the institutional review boards for participating investigators approved the study. The clinical and research activities reported here are consistent with the principles outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism (27). All clinical investigators abided by the Ethical Principles for Medical Research Involving Human Subjects as outlined in the Declaration of Helsinki.

Recipient characteristics, treatments, and outcomes were abstracted at the time of transplant, and at nine time points post-transplant: 3 months, semiannually from 6 months to 3 years, and annually from 4 to 5 years. We defined PTDM

as the documentation of diabetes in the electronic health record, having a hemoglobin A1c ≥6.5%, or being on pharmacological treatment for diabetes. PTDM status was determined for each post-transplant time interval, thus allowing PTDM status to vary over time. We calculated the kidney donor risk index for each donor and mapped resulting values to the KDPI relative to all deceased donors in the OPTN database in 2010 (28,29). KDPI was used in the analysis of PTDM risk factors as a surrogate for allograft quality.

Outcome Definitions

Longitudinal post-transplant graft outcomes were all-cause graft failure (aGF), dcGF, and all-cause mortality, and were ascertained *via* OPTN records and electronic medical records. We defined dcGF as return to dialysis or retransplantation during follow-up time, before death censoring at 5 years post-transplant. When examining all-cause mortality as an outcome, we censored at graft failure, death, or last follow-up year. We defined aGF as all-cause mortality, primary nonfunction of the allograft, return to dialysis, or retransplantation.

In supplemental analyses we also examined the outcomes of biopsy proven acute rejection and cardiovascular events. Cardiovascular events were defined as rehospitalizations in which the primary discharge diagnosis was abstracted as "cardiovascular."

Statistical Analysis

We reported descriptive statistics as mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables, and frequencies (percentages) for categorical variables. Continuous variables were compared with Wilcoxon rank-sum test, and categorical variables were compared with chi-squared tests or Fisher's exact tests. Cox proportional hazards models were used to evaluate the association between potential risk factors and the outcome of PTDM. We evaluated the following donor risk factors: sex, HCV infection, and KDPI; the following recipient risk factors at the time of transplant: age, BMI, HLA mismatches, and Black race. We compared post-KT changes in BMI between PTDM and non-PTDM groups using a Wilcoxon rank-sum test. We also compared the proportion of obese populations between PTDM and non-PTDM groups using an intraclass correlation test where obesity was defined as BMI ≥30 kg/m^2. In addition, we compared cumulative PTDM incidence on the basis of rigorous data collection in our cohort, cumulative PTDM incidence reported to UNOS for the DDS cohort, and cumulative PTDM incidence reported to UNOS for KT recipients across the country from 2010 to 2013.

Time-varying Cox proportional hazards models were used to evaluate the association of PTDM on aGF, dcGF, and all-cause mortality (30). For these time-varying analyses, in patients that developed PTDM, the time from transplant to PTDM diagnosis contributes to the nonevent. The time from PTDM to last follow-up (graft failure, death, or last follow-up year) in the OPTN data contributes as an event. We used Kolmogorov-type supremum tests to determine whether models satisfied proportional hazards assumptions (31). We accounted for the cluster effect of paired kidneys from the same donor using robust sandwich estimates. The models adjusted for KDPI, cold ischemia time, transplant center, and recipient variables of age, Black race, sex, previous KT, number of HLA mismatches, panel reactive antibody percentage, BMI, and preemptive transplant. These variables were selected on the basis of the risk factors identified in our systematic review of the literature (Supplemental Table 1) We conducted a complete case analysis because <2% of data for all covariates was missing. In a secondary analysis, we considered another definition of PTDM that included time of onset. We used time-dependent Cox proportional hazard models to explore the association of PTDM by time of onset (early-onset (diagnosed within 1 year of KT) and late-onset (diagnosed after 1 year post-KT) with the outcomes of dcGF, aGF, or all-cause mortality.

In supplemental analyses we explored the association of PTDM and time to first biopsy-proven acute rejection using the same time-varying modeling approach as for the primary analysis. Chi-squared test was used to evaluate the association between PTDM and cardiovascular events.

We used SAS 9.4 software for Windows (SAS Institute, Cary, NC, USA) for analysis. All statistical tests and confidence intervals were two sided, with a significance level of 0.05.

Results

Cohort Characteristics

Of the 1232 KT recipients from 13 participating transplant centers, 632 were eligible and included in the analysis (Figure 1). Mean recipient age was 52±14 years; 59% were male, 49% were Black, 7% were HCV seropositive, and mean BMI was 27.7±5.7 kg/m^2 at time of transplant (Table 1). In total, 60 (10%) KT recipients were preemptive. Recipients were followed by serial chart review for 4 years (IQR, 3–5). Mean donor age was 41±15 years; 16% were Black, mean BMI was 28.3±7.3 kg/m^2 at time of donation, mean

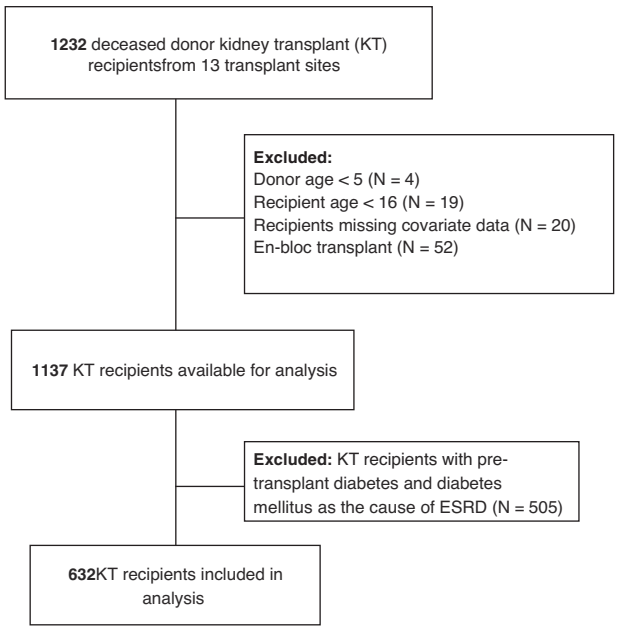


Figure 1. | **Cohort generation.**

Table 1. Recipient and transplant characteristics by post-transplant diabetes

Recipient Characteristics	Nonpost-transplant Diabetes Mellitus (*n*=446)	Post-transplant Diabetes Mellitus (*n*=186)	*P* value[a]
Age, yrs, mean (SD)	50.18 (14.34)	55.24 (12.07)	<0.001
Hispanic ethnicity, *n* (%)	42 (9)	12 (6)	0.37
Black race, *n* (%)	215 (48)	92 (49)	0.79
Male, *n* (%)	262 (59)	112 (60)	0.76
Weight, kg, mean (SD)	79.44 (19.59)	83.42 (19.86)	0.02
BMI, kg/m^2, mean (SD)	27.25 (5.76)	28.68 (5.48)	0.001
BMI <30, *n* (%)	323 (72)	116 (62)	0.05
Obesity Class 1 (BMI 30.0–34.9), *n* (%)	80 (18)	44 (24)	
Obesity Class 2 (BMI 35.0–39.9), *n* (%)	29 (7)	21 (11)	
Obesity Class 3 (BMI ≥40), *n* (%)	14 (3)	5 (3)	
Previous kidney transplant, *n* (%)	80 (18)	25 (13)	0.16
ESKD duration, months, mean (SD)	53.43 (39.04)	50.27 (36.35)	0.54
Cause of ESKD, *n* (%)			0.50
Hypertension	167 (38)	80 (43)	
Glomerulonephritis	116 (26)	40 (22)	
Graft failure	46 (10)	14 (8)	
Diabetes	2 (0)	1 (1)	
Other or unknown	114 (26)	51 (27)	
Preemptive transplant	42 (9)	18 (10)	0.93
Pre-transplant transfusions	91 (20)	25 (13)	0.07
Hepatitis C seropositive	30 (7)	14 (8)	0.85
HLA mismatches, mean (SD)	4.32 (1.33)	4.35 (1.32)	0.89
Peak panel reactive antibody, *n* (%)			0.66
0%	263 (59)	118 (63)	
1–20%	26 (6)	12 (6)	
21–80%	72 (16)	24 (13)	
>80%	84 (19)	32 (17)	
Kidney pumped, *n* (%)	218 (49)	78 (42)	0.11
Kidney biopsied, *n* (%)	228 (51)	82 (44)	0.10
Cold ischemia time, hours, mean (SD)	16.51 (7)	16.4 (6.57)	0.90

[a]Wilcoxon rank-sum test for continuous variables and chi-square test for categorical variables.

Table 2. Donor characteristics by recipient post-transplant diabetes

Donor Characteristic	Nonpost-transplant Diabetes Mellitus (*n*=446)	Post-transplant Diabetes Mellitus (*n*=186)	*P* value[a]
Age, years, mean (SD)	40.3 (15.21)	41.7 (14.49)	0.32
Hispanic ethnicity, *n* (%)	67 (15)	30 (16)	0.73
Black race, *n* (%)	73 (16)	27 (15)	0.55
BMI, kg/m^2, mean (SD)	28.3 (7.53)	28.5 (6.72)	0.37
Hypertension, *n* (%)	135 (30)	51 (27)	0.46
Diabetes, *n* (%)	48 (11)	17 (9)	0.54
DCD, *n* (%)	88 (20)	46 (25)	0.17
ECD, *n* (%)	86 (19)	29 (16)	0.27
Cause of death, *n* (%)			0.61
Head trauma	117 (27)	45 (25)	
Anoxia	160 (36)	71 (39)	
Stroke	155 (35)	64 (35)	
Other	8 (2)	1 (1)	
Admission serum creatinine, mg/dl, mean (SD)	1.1 (0.67)	1.1 (0.73)	0.69
Terminal serum creatinine, mg/dl, mean (SD)	1.2 (0.93)	1.1 (0.77)	0.32
KDRI, mean (SD)	1.3 (0.43)	1.3 (0.37)	0.86
KDPI, *n* (%)	48.3 (27)	48.6 (25)	0.86

BMI, body mass index; DCD, donation after circulatory death; ECD, expanded-criteria donor; KDRI, kidney donor risk index; KDPI, kidney donor profile index.
[a]Wilcoxon rank-sum test for continuous variables and chi-square test for categorical variables.

KDPI was 48±27%, and 10% of donors had a history of DM (Table 2).

Incidence and Risk Factors of PTDM

Of the 632 KT recipients, 186 (29%) were diagnosed with PTDM at median follow-up of 4 years (IQR, 3–5). Of those, 117 (63%) were diagnosed with PTDM within 12 months of KT (Figure 2). Within the PTDM group, 80 (43%) were treated with insulin therapy, 71 (38%) with oral antihyperglycemics, and 35 (19%) were treated with diet modification only. For the OPTN data reported to UNOS on the same recipients, PTDM was noted in 60 (9%) patients at 12 months post-KT and 89 (14%) patients by the end of the 60-month follow-up ascertainment period (Figure 2). Using data reported to UNOS on all 24,588 recipients across the country during the same time period, PTDM incidence at 12 and 60 months post-KT was 1679 (7%) and 2823 (12%), respectively (Figure 2).

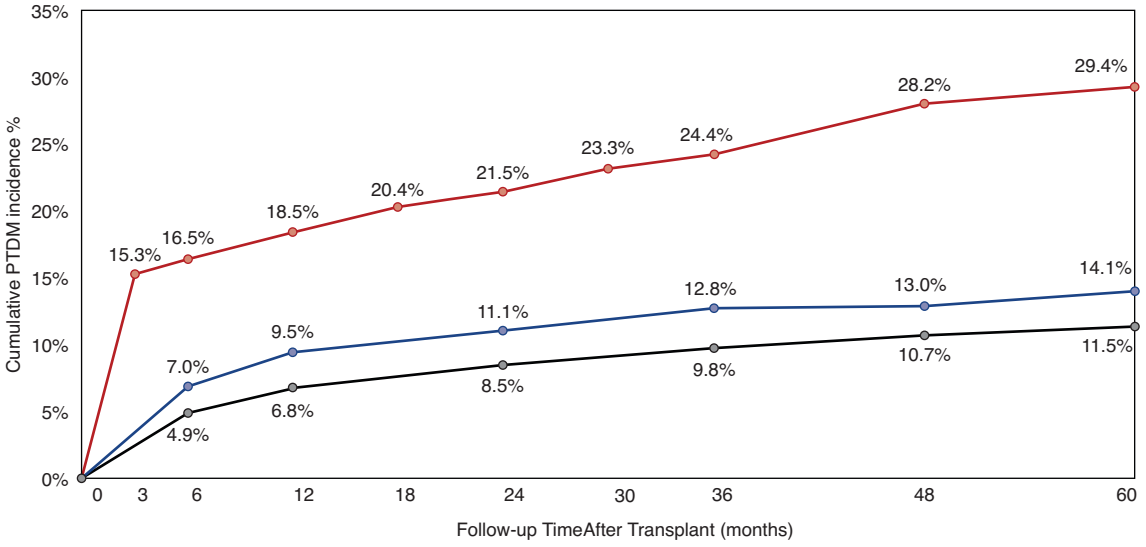
Older recipient age, higher weight, and higher BMI at transplant were associated with PTDM in univariate analyses (Table 3). Recipient race, HLA mismatches, donor HCV status, donor sex, and KDPI were not significantly associated with PTDM. Multivariable analyses revealed that older recipient age (adjusted hazard ratio [aHR], 1.14; 95% confidence interval [95% CI], 1.07 to 1.20 per 5-year increase) and higher recipient BMI (aHR, 1.19; 95% CI, 1.05 to 1.34 per 5 kg/m^2) at transplant were independent risk factors for PTDM, after adjustment for recipient Black race and HLA mismatches. At 12 months after transplant, overall median weight gain was 3.54 (IQR, -0.18–7.40) kg and change in BMI was 1.15 (IQR, -0.06–2.49) kg/m^2. During follow-up, the peak BMI and weight increase occurred within the first year after KT for both PTDM and non-PTDM groups (Figure 3 and Supplemental Figure 1). However, the median change in BMI post-KT did not differ between those with and without incident PTDM (P=0.19, Supplemental Table 2). The proportion of obese patients was higher in the PTDM group (P<0.001) throughout follow-up (Supplemental Figure 2).

Association of Immunosuppressant Therapy and PTDM

Induction immunosuppression regimens were similar between those patients with and without PTDM (Table 4). Most patients received induction therapy with both methylprednisolone and rabbit antithymocyte globulin. At 3 months post-KT, 93% of patients included in our cohort had received at least one maintenance dose of tacrolimus; 96% of the PTDM group and 92% of non-PTDM group were taking tacrolimus. Similar trends were seen at the 6- and 12-month post-KT follow-up times (Table 5). Tacrolimus trough levels (ng/ml) were similar between the PTDM and non-PTDM groups at 3, 6, and 12 months post-KT. Prednisone daily dose was also similar between groups at 3, 6, and 12 months post-KT (Table 5).

Association of PTDM and Adverse Graft Outcomes

Rates of dcGF, aGF, and all-cause mortality were similar between patients with and without PTDM (Table 6). For the PTDM group, event rates per 1000 patient-years were dcGF 32 (95% CI, 21 to 47), aGF 67 (95% CI, 51 to 88), and all-cause mortality 43 (95% CI, 31 to 60). Event rates for the non-PTDM group were dcGF 37 (95% CI, 30 to 46), aGF 58 (95% CI, 49 to 68), and all-cause mortality 28 (95% CI, 22 to 35). Results were unchanged when considering diabetes treatment type (insulin therapy, oral



DDS Cohort, DDS PTDM (n=632)	0	97	104	117	129	136	147	154	178	186
DDS Cohort, UNOS PTDM (n=632)	0	N/A	44	60	60	70	70	81	82	89
UNOS Cohort, UNOS PTDM (n=24588)	0	0	1221	1679	1679	2101	2101	2412	2641	2823

Figure 2. | **Comparison of cumulative PTDM rates between DDS Cohort and UNOS 2010-2013.** Comparison of cumulative PTDM incidence in prospective multi-center study (DDS) with data reported to UNOS for recipients in DDS cohort and data reported to UNOS for recipients across the country during the same time period.

Table 3. Donor and recipient characteristics associated with de-novo post-transplant diabetes mellitus in univariate analysis

Risk Factors	Value level	Univariate Hazard Ratio (95% Confidence Interval)[b]	Univariate *P* value	Multivariable[a] Hazard Ratio (95% Confidence Interval)
Donor risk factors				
Age	5 year increase	1.04 (0.99 to 1.09)	0.13	…
Weight (kg)	5 kg increase	1.02 (0.98 to 1.05)	0.46	…
BMI (kg/m^2)	5 unit increase	1.01 (0.92 to 1.11)	0.84	…
Obesity	Yes vs no	0.91 (0.66 to 1.24)	0.55	…
Donor KDPI	10 unit increase	1.02 (0.97 to 1.08)	0.43	…
Hepatitis C	Yes vs no	1.13 (0.46 to 2.75)	0.79	…
Recipient risk factors (at time of transplant)				
Age	5 year increase	1.12 (1.06 to 1.18)	<0.001[a]	1.14 (1.07 to 1.20)
Weight (kg)	5 kg increase	1.03 (1.00 to 1.06)	0.03	…
BMI (kg/m^2)	5 unit increase	1.18 (1.05 to 1.33)	0.006[a]	1.19 (1.05 to 1.34)
Black race	Yes vs No	1.05 (0.78 to 1.39)	0.76	1.15 (0.85 to 1.56)
HLA mismatches	1 unit increase	1.01 (0.91 to 1.13)	0.79	0.97 (0.87 to 1.09)

BMI, body mass index.
[a]From a multivariable model with recipient age, BMI, Black race, and HLA mismatch.
[b]Cox regression model; obesity defined as BMI >30 kg/m^2.

antihyperglycemics, and diet only) for the patients with PTDM. Results were unchanged after excluding patients with PTDM whose treatment was composed of diet modification only. In total, 405 (64%) patients had at least one rehospitalization within 5 years post-KT. Of these, 37 (9%) were for cardiovascular events (primary discharge diagnosis) with similar rates by PTDM status (PTDM 8 out of 122, 7%, vs non-PTDM 29 out of 283, 10%, P=0.24).

In the early-onset PTDM group (diagnosed within 1 year of KT), there were 14 dcGFs (12% event rate), 32 (27%) aGFs, and 23 (20%) deaths. In the late-onset PTDM group (diagnosed after the first year of KT), there were 11 (16%) dcGFs, 21 (30%) aGFs, and 11 (16%) deaths (Table 6). Early-

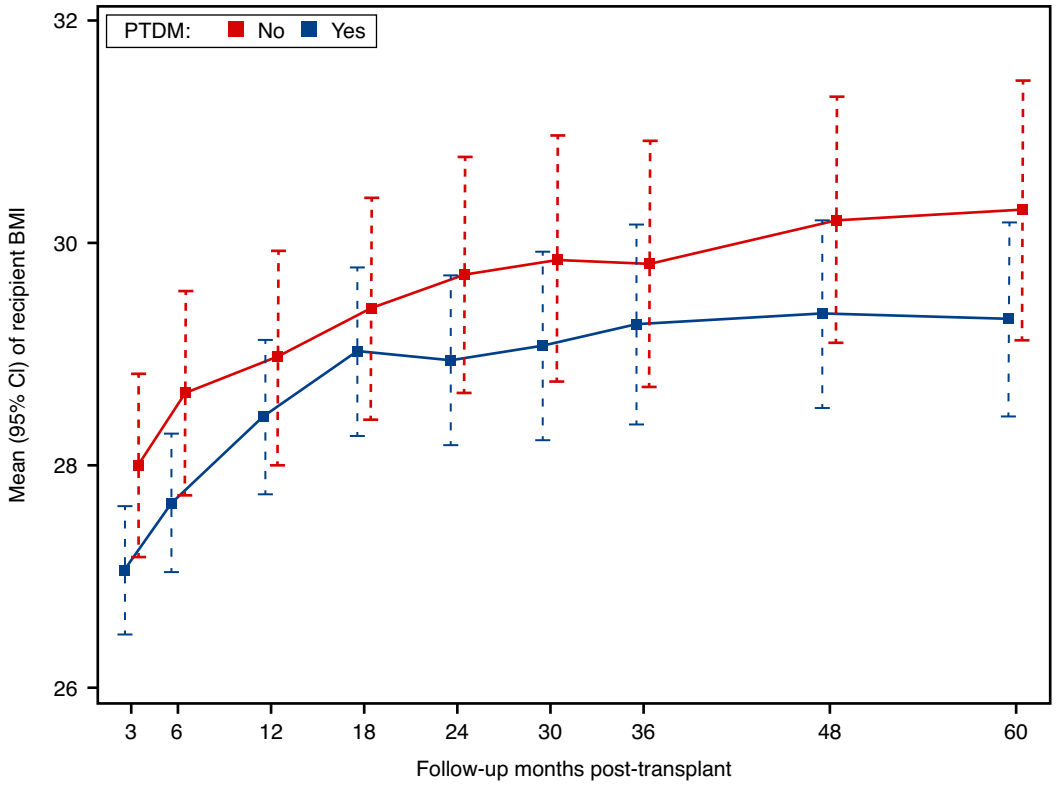


Figure 3. | Comparison of Post-KT BMI over Time between recipients who did and did not develop PTDM.

Table 4. Comparing induction therapy between PTDM and non-PTDM groups[a]

Induction Therapy[a]	No Post-transplant Diabetes Mellitus, *n* (%)	Post-transplant Diabetes Mellitus, *n* (%)
Pretransplant desensitization protocol used	29 (7)	6 (3)
Intravenous immunoglobulin	39 (9)	11 (6)
Methylprednisolone	407 (91)	177 (95)
Anti-thymocyte globulin (rabbit)	368 (83)	157 (84)
Basiliximab	64 (14)	31 (17)
Alemtuzumab	15 (3)	3 (2)
Rituximab	9 (2)	1 (1)
Experimental or other drug used for induction	7 (2)	2 (1)

[a]Induction immunosuppression was not significantly different between recipients with and without post-transplant diabetes mellitus ($P>0.05$).

onset PTDM was not associated with adverse graft outcomes (Table 6). In contrast, late-onset PTDM was a strong risk factor for dcGF (aHR, 2.14; 95% CI, 1.08 to 4.21) and aGF (aHR, 2.07; 95% CI, 1.25 to 3.44). Late-onset PTDM was not independently associated with all-cause mortality (aHR, 1.91; 95% CI, 0.93 to 3.92).

Supplemental Table 3 summarizes time to first biopsy-proven acute rejection between the PTDM and non-PTDM groups. After adjusting for donor and recipient factors, there was a four-fold higher association of time to first biopsy-proven acute rejection in the PTDM group (Supplemental Table 3). Of the 97 patients with biopsy-proven acute rejection, 63 (65%) received methylprednisolone. Steroid treatment after acute rejection was similar between patients that did and did not develop diabetes (Supplemental Table 4).

Discussion

In this multicenter cohort study of KT recipients of deceased-donor kidneys, we found that PTDM occurred commonly with a cumulative incidence of nearly 30% over a 5-year follow-up period. Risk factors for PTDM suggested by prior studies, such as increased HLA mismatches, HCV infection, race, and ethnicity, and male donor status were not found to be associated with PTDM in our cohort. Furthermore, we identified only modest associations for older recipient age and BMI at transplant with the development of PTDM. We also identified a four-fold higher association of acute rejection with PTDM in our cohort. Although we did not identify any significant associations between PTDM and graft failure or mortality, in subgroup analyses, late-onset PTDM (developing beyond 1 year after KT) was associated with worse graft outcomes.

Weight gain is common among recipients after KT (17,32,33). We found that KT recipients with or without PTDM generally experienced similar weight changes. We compared BMI trends between groups before or after the first year post-KT. We found that within the first year, BMI increased to a greater extent than it did after 1 year post-KT for both groups. Although higher baseline BMI was weakly associated with PTDM, BMI trends after KT were not, which may be because other more significant factors come into play after KT, such as immunosuppression.

Previous studies have found PTDM to be associated with reduced graft survival (2–6,32). We did not find a strong association between PTDM and aGF, dcGF, or all-cause mortality, which may be due to limited statistical power and follow-up time after PTDM that may be too short to detect a relationship. However, associations between PTDM and graft outcomes in our cohort differed on the basis of early-onset (diagnosed within the first year) and late-onset (diagnosed after 1 year post-KT) PTDM. Although early-onset PTDM was not associated with adverse graft outcomes, late-onset PTDM was strongly associated with aGF and dcGF. Although multivariable models included several important donor and recipient characteristics, it remains unclear whether these adverse graft outcomes are attributable to PTDM or other risk factors for graft failure over a prolonged period, such as drug nonadherence, post-transplant hypertension, recurrent glomerular disease, or gene polymorphisms (34). In our cohort, we found that although PTDM was associated with graft rejection, there was no association between PTDM and methylprednisolone treatment (Supplemental Tables 3 and 4). Graft rejection, depending on severity, is managed by administration of thymoglobulin or escalating the dose of baseline immunosuppressive medications, such as tacrolimus, which could not be fully ascertained in this study. It is also likely that presence of PTDM itself may contribute to increased acute rejection risk due to activation of innate immunity, proinflammatory cytokines, or other biologic mechanisms (35).

Over time, many new therapies for PTDM have been introduced, and it is likely that greater focus on this issue has been applied by transplant clinicians in recent years. However, although short-term graft survival has improved in the last decade, such improvements have not substantially changed long-term graft outcomes (34).

Our 13 participating centers reported to UNOS roughly half (14%) of the patients with PTDM that we ascertained (29%) with careful chart review for the same group of patients by the end of the 60-month follow-up. In addition, when assessing outcomes of all 24,588 KT recipients in the United States within the OPTN database during the same period of time, UNOS-reported PTDM incidence 60 months after KT was only 12%. This may indicate that PTDM is being underreported across multiple (if not all) centers and may be

Table 5. Comparing maintenance immunosuppression between PTDM and non-PTDM groups

	At Discharge		3 months		6 months		12 months		Within 12 months	
Maintenance Immunosuppression	No Post-transplant Diabetes Mellitus	Post-transplant Diabetes Mellitus	No Post-transplant Diabetes Mellitus	Post-transplant Diabetes Mellitus	No Post-transplant Diabetes Mellitus	Post-transplant Diabetes Mellitus	No Post-transplant Diabetes Mellitus	Post-transplant Diabetes Mellitus	No Post-transplant Diabetes Mellitus	Post-transplant Diabetes Mellitus
Tacrolimus	423 (95%)	181 (97%)	411 (92%)	179 (96%)	382 (90%)	176 (96%)	374 (89%)	171 (94%)	420 (94%)	181 (97%)
Dose, mg/day	10 (6, 12)	8 (6, 12)	8 (6, 12)	8 (5, 12)	7 (4.75, 12)	6 (3.5, 10.5)	6 (4, 10)	5 (3, 9)	7.5 (5, 11)	6 (4.3, 10.7)
	n=422	*n*=179	*n*=408	*n*=178	*n*=376[a]	*n*=176[a]	*n*=368	*n*=171	*n*=416[a]	*n*=181[a]
Trough	6.3 (4.1, 8.8)	6.45 (3.6, 9)	8.4 (6.9, 10.1)	8.7 (6.9, 11)	7.4 (5.9, 9.1)	7.1 (6.1, 8.9)	6.5 (5.3, 7.8)	6.5 (5.3, 7.8)	7.6 (6.5, 8.9)	7.7 (6.6, 8.8)
	n=408	*n*=178	*n*=406	*n*=178	*n*=377	*n*=175	*n*=369	*n*=171	*n*=418	*n*=181
Mycophenolate	429 (96%)	183 (98%)	410 (92%)	173 (93%)	345 (81%)	155 (84%)	327 (78%)	147 (81%)	421 (94%)	178 (96%)
Dose	1440 (1000, 2000)	1440 (1000, 2000)	1080 (1000, 1500)	1290 (1000, 1500)	1000 (1000, 1440)	1080 (1000, 1440)	1000 (1000, 1440)	1000 (720, 1440)	1080 (960, 1440)	1080 (960, 1440)
	n=429	*n*=183	*n*=410	*n*=172	*n*=346	*n*=155	*n*=327	*n*=147	*n*=421	*n*=178
Sirolimus	3 (1%)	0	10 (2%)	2 (1%)	6 (1%)	1 (1%)	9 (2%)	3 (2%)	16 (4%)	4 (2%)
Dose, mg/day	3.0 (0, 9)	…	3.25 (2, 6)	3 (3, 3)	5.5 (2.5, 7)	8 (8, 8)	3 (1,4)	4 (3, 4)	3.25 (2, 5)	4 (3, 4.67)
			n=10	*n*=2	*n*=6	*n*=1	*n*=9	*n*=3	*n*=14	*n*=3
Trough, ng/ml	4.0 (0, 9)	….	5.2 (3.7, 8.1)	7 (3.5, 10.5)	7.85 (5.6, 9.82)	6 (6, 6)	8.2 (5.1, 11.5)	8.35 (7.6, 9.1)	7.8 (3.8, 10.38)	7.6 (6.2, 10.5)
			n=9	*n*=2	*n*=6	*n*=1	*n*=9	*n*=2	*n*=16	*n*=3
Everolimus	0	0	1 (0%)	0	1 (0%)	1 (1%)	2 (0%)	1 (1%)	2 (0%)	1 (1%)
Dose	…	…	3	….	5	0	4 (3,4)	6	3 (3,4)	4
Belatacept	2 (0%)	0	3 (1%)	0	4 (1%)	0	4 (1%)	0	4 (1%)	0
Prednisone	368 (84%)	165 (91%)	364 (82%)	163 (88%)	341 (80%)	159 (86%)	338 (81%)	156 (86%)	375 (84%)	166 (89%)
Dose ≤5	Median (IQR)	Median (IQR)	243 (68%)	120 (75%)	283 (83%)	138 (87%)	300 (89%)	141 (90%)	236 (63%)	112 (67%)
Dose >5	20 (20, 30)	20 (20, 55)	117 (33%)	41 (25%)	58 (17%)	21 (13%)	38 (11%)	15 (10%)	137 (37%)	54 (33%)
	n=356	*n*=164								
Cyclosporine	8 (2%)	3 (2%)	10 (2%)	3 (2%)	16 (4%)	4 (2%)	18 (4%)	5 (3%)	20 (4%)	5 (3%)
Dose, mg/day	312.5 (150, 575)	550 (350, 650)	250 (200, 400)	400 (300, 400)	250 (200, 300)	350 (275, 375)	200 (150, 250)	250 (200, 275)	229.17	283.33
	n=8	*n*=3	*n*=10	*n*=3	*n*=16	*n*=3	*n*=18	*n*=5	(168.75, 304.17)	(200, 333.33)
									n=20	*n*=5
Trough, ng/ml	65.5 (29, 314)	148 (66.5, 186.6)	279 (204, 349)	192 (167.4, 227)	162.65 (129, 237.3)	148.5 (131.9, 165.45)	171.9 (96, 214)	148 (117, 173)	182.67	168.33
	n=8	*n*=3	*n*=9	*n*=3	*n*=14	*n*=4	*n*=15	*n*=5	(147.45, 228.67)	(158.67, 173)
									n=17	*n*=5

Results are similar between those that developed post-transplant diabetes mellitus and those that did not, unless indicated. IQR, interquartile range.
[a] $P \leq 0.05$.

Table 6. Association of post-transplant diabetes mellitus with adverse graft outcomes

Exposure		Death-censored Graft Failure				All-cause Graft Failure				All-cause Mortality			
		n (%)	Event rate per 1000 Person-years	Unadjusted Hazard Ratio (95% Confidence Interval)	Adjusted[a] Hazard Ratio (95% Confidence Interval)	*n* (%)	Event rate per 1000 Person-years	Unadjusted Hazard Ratio (95% Confidence Interval)	Adjusted[a] Hazard Ratio (95% Confidence Interval)	*n* (%)	Event rate per 1000 Person-years	Unadjusted Hazard Ratio (95% Confidence Interval)	Adjusted[a] Hazard Ratio (95% Confidence Interval)
A	No PTDM (*n*=446)	93 (21)	37 (30, 46)	1 (ref)	1 (ref)	145 (33%)	58 (49, 68)	1 (ref)	1 (ref)	70 (16%)	28 (22, 35)	1 (ref)	1 (ref)
	PTDM (*n*=186)	25 (21)	32 (21, 47)	0.92 (0.58 to 1.48)	0.85 (0.53 to 1.37)	54 (28%)	67 (51, 88)	1.23 (0.89 to 1.70)	1.10 (0.78 to 1.55)	34 (18%)	43 (31, 60)	1.56 (1.03 to 2.38)	1.31 (0.84 to 2.05)
B	No PTDM (*n*=446)	93 (21)	37 (30, 46)	1 (ref)	1 (ref)	145 (33%)	58 (49, 68)	1 (ref)	1 (ref)	70 (16%)	28 (22, 35)	1 (ref)	1 (ref)
	Early-onset PTDM[b](*n*=117)	14 (12)	23 (14, 39)	0.70 (0.40 to 1.23)	0.56 (0.31 to 1.04)	32 (27%)	53 (37, 74)	0.98 (0.66 to 1.44)	0.85 (0.57 to 1.28)	23 (20%)	38 (25, 57)	1.39 (0.86 to 2.24)	1.16 (0.70 to 1.91)
	Late-onset PTDM[b] (*n*=69)	11 (16)	62 (34, 112)	1.86 (0.97 to 3.59)	2.14 (1.08 to 4.21)	21 (30%)	118 (77, 182)	2.09 (1.29 to 3.37)	2.07 (1.25 to 3.44)	11 (16%)	62 (34, 112)	2.20 (1.13 to 4.27)	1.91 (0.93 to 3.92)

PTDM, post-transplant diabetes mellitus; KDPI, kidney donor profile index.

[a]Adjusted models include donor KDPI, cold ischemia time and the following recipient variables: age (years), Black race, sex, previous kidney transplant, number of human leukocyte antigen mismatches, panel reactiveantibody (%), body mass index (kg/m^2), preemptive transplant, and transplant center.

[b]Early diabetes is new onset diabetes within 1 year post-transplant, whereas late diabetes is new onset diabetes after 1 year post-transplant.

a shortcoming that would benefit from standardized data capture and training.

Our study has several strengths. We collected data from 13 US transplant centers, including academic and nonacademic centers, thus capturing a variety of post-transplant processes of care. Many prior studies used billing codes or were registry based, but we utilized detailed chart review to obtain reliable estimates of cumulative incidence. This multicenter study is likely more generalizable than many prior single-center studies (Supplemental Table 1) (2,3,9–11,13,15, 20,21,36–47). Many studies defined PTDM using the 2003 International Consensus Guidelines on the basis of recommendations of the ADA (18). Some groups also used extended PTDM diagnostic criteria that include administration of antihyperglycemic agents and updated ADA recommendations, such as hemoglobin A1c ≥6.5%. Despite variability in clinical practice, our multicenter study applied the same diagnostic criteria (hemoglobin A1c ≥6.5%, diabetes treatment, or documentation of diabetes in the electronic medical record), and coordinators entered data on diabetes diagnosis in a consistent manner. Although International Consensus Guidelines declare the first 6 months as a critical time, during which patients are at the greatest risk of developing PTDM, the guidelines do not establish a limit on the time since transplantation when diabetes should be declared PTDM versus type 2 DM (18). We began ascertaining PTDM criteria immediately after KT and <5 years post-transplant. Standardized data collection at several time points for PTDM diagnosis across the 13 sites by trained research coordinators may have allowed our study to better capture the cumulative incidence of PTDM compared with what these centers reported to UNOS.

In terms of study limitations, 86% of patients in our cohort received prednisone within 12 months after KT. No association between the use of steroids, a modifiable risk factor, and the development of PTDM could be deduced due to underpowered analyses. Additional multicenter studies of transplant programs that utilize steroid-free immunosuppression regimens may help better evaluate this relationship. Prior studies have also demonstrated an association between tacrolimus and PTDM, whereas other studies found no such association (4,7,40,43,48). Importantly, 95% of patients in our cohort received tacrolimus within the first year after KT, and no association between its use and the development of PTDM could be established. In addition, Figure 3 and Supplemental Figure 1 demonstrate no significant differences in BMI or weight gain after transplant by PTDM status in our cohort; however, analyses may be underpowered to detect small differences between the two groups. Overall, <1% of patients in our cohort were administered belatacept after PTDM, and thus, we were unable to explore the effect of conversion from calcineurin inhibitors to belatacept on post-KT outcomes. In addition, we lacked sufficient hemoglobin A1c data for all patients in our cohort, which precluded analyses for associations between hemoglobin A1c values and post-KT outcomes.

Although most recent studies of PTDM after KT have been single center, ours is a contemporary multicenter study highlighting practices and trends across 13 transplant centers. In conclusion, PTDM remains a frequent complication experienced by KT recipients. Modifiable risk factors such as weight gain and immunosuppression medications were similar between patients who did and did not develop diabetes. PTDM was not associated with aGF, dcGF, or all-cause mortality at a median follow-up of 6 years. However, we found that late-onset PTDM, developing beyond the first year of transplantation, may contribute to worse graft outcomes.

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Author Contributions

R.F. Malik drafted the manuscript; Y. Jia was responsible for the statistical analyses; E. Akalin, S. Alasfar, J.S. Bromberg, M.D. Doshi, I.E. Hall, M.N. Harhay, S.G. Mansour, S. Mohan, T. Muthukumar,

P.P. Reese, B. Schröppel, P. Singh, H. Thiessen Philbrook, and F.L. Weng reviewed and edited the manuscript; E. Akalin, S. Alasfar, J.S. Bromberg, M.D. Doshi, I.E. Hall, M.N. Harhay, R.F. Mal ik, S.G. Mansour, S. Mohan, T. Muthukumar, C.R. Parikh, P.P. Reese, B. Schröppel, P. Singh, and F.L. Weng were responsible for interpreting results; M.D. Doshi was responsible for the study design; E. Akalin, J.S. Bromberg, M.D. Doshi, M.N. Harhay, S. Mohan, T. Muthukumar, P.P. Reese, B. Schröppel, P. Singh, and F. L. Weng were responsible for contributing study subjects for the parent study; H. Thiessen Philbrook was responsible for important statistical feedback; and C.R. Parikh conceptualized the parent study, participated in the design of this study, and helped write the manuscript.

Supplemental Material

This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0000862021/-/DCSupplemental.

Supplemental Appendix A. Data quality description.

Supplemental Figure 1. Comparison of post-KT weight over time between recipients who did and did not develop PTDM.

Supplemental Figure 2. Comparing proportion of obese (BMI >30 kg/m^2) patients between recipients who did and did not develop PTDM.

Supplemental Table 1. Summary of PTDM definitions from literature, 2009–2019.

Supplemental Table 2. Association of BMI/weight trajectory and PTDM.

Supplemental Table 3. Association of biopsy-proven acute rejection (time to first biopsy proven rejection) and PTDM.

Supplemental Table 4. Methylprednisolone administration and PTDM development among patients with biopsy-proven acute rej ection.

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