ORIGINAL ARTICLE

Long-term patient survival and kidney allograft survival in post-transplant diabetes mellitus: a single-center retrospective study

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SUMMARY

A decade ago, observations suggested that post-transplant diabetes mellitus (PTDM) was linked to allograft loss and shorter patient survival. Increasing awareness, improvements in care, and changes in the immunosuppressive regimen may have modified this association. Single-center analysis of 1990 (age>18; transplantation date 1996–2012) primary kidney recipients (KTR). Patients with <12 months follow-up were excluded. Diabetes was diagnosed according to ADA criteria and characterized as follows: No diabetes, PTDM in the first post-transplant year not treated with glucose-lowering medications (GLM) at 12 months, PTDM in the first post-transplant year treated with GLM at 12 months, and pretransplant diabetes. Cox proportional hazards models were used to examine the relationship of PTDM with allograft and patient survival. Mean follow-up time was 6.8 years for allograft survival and 7.4 years for patient survival. PTDM treated with medication at year one was not associated with allograft survival (HR 1.28, 95% CI 0.97–1.69), but was significantly associated with overall mortality and death with functioning graft (DWFG) (HR overall: 1.81, 95% CI 1.36–2.39; HR DWFG: 1.59 95% CI 1.05–2.38). In this cohort, KTR with PTDM being treated with glucose-lowering medication at 12 months experienced significantly shorter overall survival and survival with functioning graft.

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Key words
diabetes, kidney transplantation, long term complications

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Introduction

Pretransplant diabetes mellitus (DM) in kidney recipients is associated with increased risk for cardiovascular disease, a higher mortality rate, and shorter allograft survival [1–3].

Early research investigating post-transplant diabetes mellitus (PTDM) did not show significant associations with patient [4–6] or allograft survival [4,7]. However, these studies had small sample sizes, varying definitions of PTDM, or were not primarily designed to detect these associations. These study cohorts comprised recipients largely transplanted prior to use of contemporary immunosuppression including current induction regimens, tacrolimus, and mycophenolate-based maintenance therapy and were characterized by higher acute rejection rates than has been observed over the past 15 years.

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In 2002, Cosio *et al.* [8] reported an association between PTDM and patient survival, but no association with allograft survival. A registry data analysis, where the diagnosis of PTDM was based on Medicare claims, subsequently demonstrated associations of PTDM with reduced patient and reduced allograft survival [9].

More than a decade has passed since these important publications. Besides greater awareness of this complication, more efficacious immunosuppression with differing risks of PTDM has since been utilized. PTDM risk factors like elevated BMI and older age have also become more prevalent among wait-listed patients [10]. Perhaps, in part, because of these changes, recent studies have not uniformly demonstrated different patient and allograft outcomes in recipients with PTDM compared to those without diabetes in the United States [11–13]. In contrast, a Norwegian single-center study reported an independent association between PTDM and patient survival, but not with allograft survival; however, 90% of patients in this study were receiving cyclosporine A-based immunosuppression [14].

The reasons for recent studies' inability to link PTDM to premature allograft loss are unclear, but may be variably related to limited sample size, insufficient follow-up time, or inconsistencies in the definition of PTDM. As with type 2 diabetes, the detrimental effects of PTDM may need prolonged time to develop, so short follow-up times may not be sufficient to detect an effect on important clinical outcomes. Over the past decade, more widespread use of tacrolimus and lymphocyte depleting agents and more widespread use of cardiovascular preventive therapies may have improved post-transplant allograft and patient survival, which might mitigate the negative health consequences of PTDM. Finally, imprecise definitions of PTDM might dilute the apparent impact of this complication. For example, although transient hyperglycemia is a known predictor of PTDM, universally labeling all recipients with transient hyperglycemia as PTDM may reduce the association of PTDM with adverse outcomes [15].

Using the clinical experience of a large US transplant center that entailed contemporary immunosuppression and cardiovascular risk reduction strategies, the objective of this study was to examine the association between PTDM and both allograft and patient survival during prolonged follow-up using carefully controlled clinical definitions. Furthermore, we sought to explore the importance of severity of PTDM and time post-transplant on clinical outcomes.

Methods

Study participants

Recipients (aged >18 years) who received their first kidney transplant at the Hospital of the University of Pennsylvania between January 1, 1996 and December 31, 2012 comprised the study population. This time frame was chosen due to the fact that after 1996 follow-up data were electronically accessible and records were relatively complete. The cohort included recipients with a functioning transplant for at least one year, as well as sequential and simultaneous multi-organ recipients. Patients with allograft loss, death, or those lost to follow-up within the first post-transplant year were excluded (Fig. 1). For the analysis of the determinants of PTDM and for the survival analysis, patients with pretransplant diabetes were excluded. The institutional review board of the University of Pennsylvania approved the study protocol.

Variables of interest

Patient medical records were reviewed by trained abstractors to obtain information on age, race, gender, primary renal disease, smoking status, pretransplant diabetes, PTDM and new use of glucose-lowering medication, cardiovascular disease, immunosuppressive drugs at transplant, aspirin use at transplant, acute rejection within the first 12 months, delayed allograft function, primary nonfunction, infection with BK virus or CMV during the first 12 months, estimated GFR 6 months after transplantation, date and cause of kidney failure and death.

All patients were matched to a United Network for Organ Sharing (UNOS) dataset that provided additional recipient, donor, and transplant characteristics, including hepatitis C virus (HCV) status, BMI at transplant, PRA and number of HLA-DR mismatches, cold ischemia time, pretransplant dialysis duration, preemptive transplantation. Donor characteristics included age, race, gender, type (deceased or living).

Definitions

Four clinical outcomes were defined including: (i) overall allograft loss, (ii) allograft loss censored for death, (iii) all-cause death, and (iv) death with functioning allograft. Overall allograft loss was defined as loss of allograft due to any reason including death. Death-

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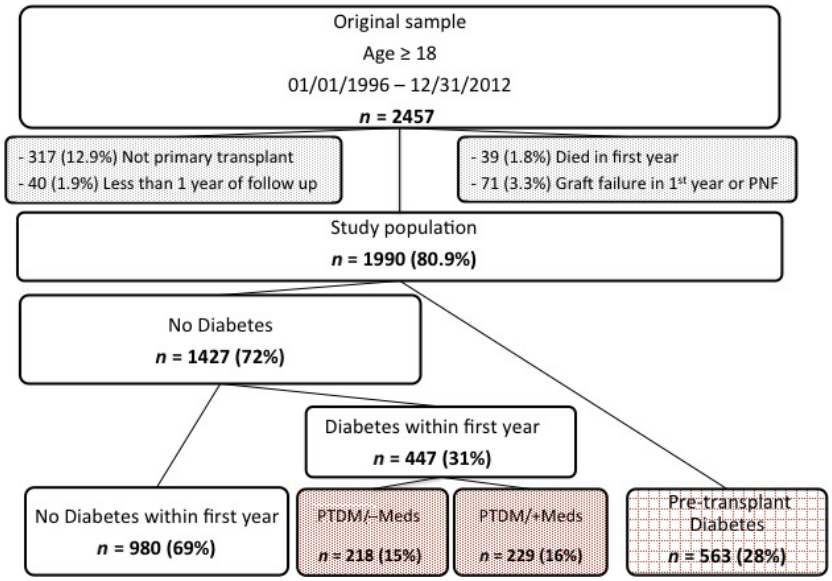

Figure 1 Flow chart for the selection of patients in this study. Diabetes within first year: Patients who met ADA criteria for diabetes during the first year after transplantation. PTDM/-Meds: transplant recipients with ADA criteria PTDM without medication at 1 year. PTDM/+Medication: transplant recipients with ADA criteria PTDM and glucose-lowering medication as an outpatient during or at year 1. PNF = primary non-function.

censored allograft loss (DCGL) included all events of allograft loss except death. All-cause mortality was defined as death from any cause, and death with functioning allograft (DWFG) indicated death at a time when the allograft was still functioning. PTDM was defined using ADA criteria as proposed elsewhere [16]. Patients were stratified into one of four groups according to diabetes status at 1 year post-transplant: (i) No diabetes (NoDM [1]), (ii) developed PTDM during the first post-transplant year, but not receiving glucose-lowering medications (GLM) at one year post-transplant (PTDM/-Meds [2]), (iii) developed PTDM in the first post-transplant year and receiving GLM at one year post-transplant (PTDM/+Meds [3]), and (iv) pretransplant diabetes (DM [4]).

We used this approach because allograft loss or death within the first 12 months is likely not related to PTDM and because we did not have the exact dates of PTDM onset. Patients without a glucose metabolism impairment during their first post-transplant year but who were started on GLM any time thereafter were analyzed in the NoDM group. Patients in the PTDM/-Meds group who were started GLM after year 1 were retained within the PTDM/-Meds group for the purpose of analysis (see Fig. 1).

Pretransplant diabetes was identified using ADA criteria [16]. Combined kidney–pancreas recipients were included in the DM group.

Rejection was defined as evidence of acute humoral or cellular rejection according to Banff criteria on a renal biopsy pathology report. The eGFR was estimated using the MDRD formula. Allograft failure was defined by the date of re-establishment of chronic dialysis therapy, re-transplant, or death.

Statistical analysis

STATA 12.1 (StataCorp LP, College Station, TX, USA) was used for all statistical analyses. A P-value <0.05 was considered statistically significant, all tests were two tailed. Nonimputed descriptive data are presented as means (SD) for continuous variables or frequencies for count data. Two-sided Student's t-test, with adjustment for unequal variances where appropriate, or the Wilcoxon rank sum test was used to examine differences between groups. Kaplan–Meier curves and the log-rank test were used to examine unadjusted differences in patient and allograft survival between the groups.

Some variables in the dataset had missing values: DR mismatch (1.0%), CMV status (4.3%), CMV disease (2.3%), preemptive transplant (1.0%), dialysis vintage (11%), cold ischemia time (19.6%), rejection (9.2%), eGFR at 6 months (6.5%), delayed allograft function (10.0%), and cardiovascular disease (2.3%). Using STATA's chained function, multiple imputation was used to generate 10 iterations for the variables each containing

1990 complete cases. The variables diabetes, transplant date, race, gender, age, HCV status, PRA, renal disease, cause, use of tacrolimus, and live donor were used as predictors during the imputation process.

Using Cox proportional hazards models, the associations of PTDM with both allograft and patient survival were estimated. Models were fit for the outcomes of allograft loss overall, death-censored allograft loss (DCGL), all-cause mortality, and death with functioning allograft (DWFG). Log-log plots and STATA's phtest were used to look for violations of the proportional hazards assumption. Using STATA's tvc (time varying covariate) option, multiple models were assessed to identify a possible PTDM-by-time interaction.

All models were adjusted for age, gender, BMI, and race. Established risk factors for the different outcomes (acute rejection in the first post-transplant year, HCV, eGFR at 6 months, DR mismatch, delayed allograft function, cold ischemia time, glomerulonephritis as cause of ESRD, pretransplant cardiovascular disease, dialysis duration (coded as no dialysis vs. ≤1 year vs. >1 year), live donor, donor age, CMV disease, and year of the transplant were included into the models. Because of the long follow-up period, we also intended to include variables that marked different immunosuppression protocol eras as well as eras for CMV prophylaxis and BK detection. Due to high correlations among these variables, only the variable accounting for tacrolimus use at the time of transplant was chosen for the final model. A sensitivity analysis included a competing risk analysis based on the Fine and Gray proportional subhazards model for overall allograft loss and the competing event of death.

Results

Cohort characteristics

During the study period, 2457 patients received a kidney transplant at our institution. We excluded 317 prior kidney recipients, 39 patients who died within the first post-transplant year, 33 patients with primary nonfunction, 38 patients with allograft failure between 3 and 12 months post-transplant, and 40 patients whose follow-up was <12 months after transplant. A total of 1990 patients remained in the cohort (Fig. 1).

Patients who died or who lost their allograft within the first year were more likely to be diabetic (41.1% vs. 28.1% $P < 0.01$), African American (47.7% vs. 33.6%, $P < 0.01$), and to have had delayed allograft function (56.3% vs. 23.6%, $P < 0.001$). There were no differences regarding age, gender, cold ischemia time, PRA, DR mismatch, ECD donor status, preemptive transplantation, or duration of dialysis treatment.

Participant characteristics

In the study population that survived at least one year after transplantation, the prevalence of pretransplant diabetes was 28% (563 of 1990). PTDM prevalence was 31% (447 of 1427) (Fig. 1). Among the patients with PTDM, 51% were being treated with GLM 12 months after transplant (group PTDM/+Meds). Of the 215 PTDM/-Meds patients, 55 started GLM beyond year 1. Over the course of the follow-up period beyond year 1, 22 patients in the NoDM group were started on GLM (not shown).

The characteristics of the cohort stratified by glycemic control are summarized in Table 1. Except for a higher rate of pretransplant cardiovascular disease, the PTDM/-Meds recipients did not differ significantly from the group without diabetes. Compared to nondiabetic patients, PTDM/+Meds recipients were older and had a higher BMI, higher rate of pretransplant CVD, and more HLA-DR mismatches. They were also less likely to have received a living donor transplant and more likely to have experienced acute rejection and DGF. Mean follow-up time was 6.8 years for allograft survival and 7.4 years for patient survival.

Outcomes

Numbers and proportions of outcomes by diabetes status are provided in Table 2.

Between January 1996 and December of 1998, 48.3% of patients received tacrolimus as maintenance calcineurin inhibitor; induction therapy consisted of eATG (16.5), basiliximab (4%), OKT3 (11%), while 67% received no induction therapy. The induction agent could not be identified for two patients. From January 1999 onwards, a maintenance immunosuppressive regimen consisting of tacrolimus, mycophenolate, and prednisone has been used for 97.1% of recipients. The remaining 2.9 percent received a regimen that did not include tacrolimus, but still included prednisone and mycophenolate. Over this period, induction with rATG has been used in 83% of recipients, basiliximab in 10.6%; 6% received no induction therapy, and the induction regimen could not be identified for 4 patients.

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Table 1. Values are given as mean (standard deviation) or number (percentage). Comparisons between no diabetes and PTDM+, no diabetes and PTDM+/Meds, and no diabetes and pretransplant diabetes.

	No diabetes $n = 980$	PTDM/-Meds $n = 218$	PTDM/+Meds $n = 229$	Pretransplant diabetes $n = 563$
Male	551 (56.2%)	126 (57.8%)	143 (62.4%)	373 (66.2%)***
Age	46.3 (13.3)	49.8 (13.8)	53.5 (11.1)***	52.2 (11.3)***
Age group (years)			***	***
<35	226 (23.0%)	38 (17.4%)	44 (7.8%)	44 (7.8%)
35–49	334 (34.1%)	56 (25.6%)	68 (27.9%)	156 (27.7%)
50+	419 (42.8%)	124 (56.8%)	148 (64.6%)	362 (64.4%)
African American	302 (30.8%)	65 (29.8%)	95 (41.4%)	210 (37.3%)**
BMI (kg/m^2)	26.1 (5.2)	26.2 (5.1)	28.5 (5.6)***	28.2 (5.4)***
BMI category			***	***
<25	437 (46.4%)	100 (47.3%)	60 (27.0%)	161 (29.7%)
≥25–<30	316 (33.6%)	65 (30.8.6%)	77 (34.6%)	185 (34.2%)
≥30	187 (19.8%)	46 (21.8%)	85 (38.2%)	195 (36.0%)
CVD +	233 (24.7%)	89 (41.2%)***	90 (40.6%)***	248 (45.0%)***
PRA				
0–≤20%	617 (90.3%)	157 (89.2)	152 (89.9%)	353 (90.0%)
>20–100%	66 (9.6%)	19 (10.8%)	17 (10.6%	39 (9.9%)
DR- mismatch			**	***
0	247 (25.3%)	51 (23.6%)	46 (20.0%)	108 (19.2%)
1	461 (47.3%)	93 (43.0%)	100 (43.6%)	241 (43.0%)
2	265 (27.2%)	72 (33.3.2%)	83 (36.2%)	211 (37.6%)
CMV status				
D-/R-	229 (24.1%)	41 (18.9%)	35 (15.4%)	129 (25.1%)
D+/R+	283 (29.8%)	75 (34.7%)	92 (40.7%)	166 (32.3%)
D-/R+	191 (20.1%)	49 (22.6%)	56 (24.7%)	114 (22.2%)
D+/R-	244 (25.7%)	51 (23.6%)	43 (19.0%)	104 (20.2%)
Preemptive transplant	221 (22.5%)	56 (25.6%)	40 (17.4%)	118 (20.9%)
Dialysis vintage (month)	27.8 (37.1)	25.8 (37.1)	29.0 (30.6)	24.0 (25.6)*
Donor age (y)	39.3 (15.0)	40.0 (14.7)	41.0 (15.4)	39.5 (15.7)
Donor age category				
<50	706 (72.1%)	152 (69.7%)	154 (67.2%)	384 (68.3%)
50+	273 (27.8%)	66 (30.2%)	75 (32.7%)	178 (31.6%)
Cold ischemia time (h)	16.3 (7.7)	16.6 (8.8)	16.5 (6.4)	14.6 (6.7)***
Living donor	375 (38.2%)	83 (38.0%)	60 (26.2%)*	133 (23.6%)***
ECD donor	101 (16.6%)	31 (22.6%)	38 (22.0%)*	96 (22.2%)*
Rejection	52 (5.7%)	17 (8.3%)	23 (11.1%)**	32 (6.4%)
HCV +	53 (5.4%)	26 (11.9%)	31 (13.5%)	73 (12.9%)*
eGFR at 6 months (ml/min)	58.5 (20.7)	60.0 (21.8)	56.5 (20.7)	57.2 (19.8)
DGF	216 (24.2%)	49 (24.8%)	72 (34.8%)*	155 (31.1%)*
Tacrolimus use at transplant	875 (89.2%)	195 (89.4%)	205 (89.4%)	539 (95.7%)

DGF, delayed allograft function; CVD, cardiovascular disease (at the time of transplant); HCV, hepatitis C virus; PTDM+, post-transplant diabetes in the first transplant year NOT treated with glucose-lowering medications; PTDM+/Meds, post-transplant diabetes in the first transplant year treated with glucose-lowering medications.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Overall allograft loss and death-censored allograft loss (DCGL)

Kaplan–Meier curves for overall allograft loss by diabetes group are shown in Fig. 2. Patients in the PTDM/-Meds, the PTDM/+Meds group, and the DM group had significantly shorter overall allograft survival after one year than patients without diabetes (log-rank P-value <0.01 for PTDM/-Meds, $P < 0.001$ for PTDM/+Meds, $P < 0.01$ for DM, Fig. 2). After adjustment by Cox proportional hazards analysis (Table 3), there was no significant difference in allograft survival between the PTDM/-Meds or the PTDM/+Meds group and the NoDM group (PTDM/-Meds: HR 1.16, 95% CI 0.88–

Table 2. Outcomes over entire observation period in absolute values and percentages by diabetes status.

	No diabetes n = 980	PTDM/-Meds n = 218	PTDM/+Meds n = 229	Pretransplant diabetes n = 563
All-cause mortality	146 (14.9%)	55 (25.2%)	66 (28.8%)	127 (22.5%)
DWFG	82 (10.2%)	34 (19.3%)	46 (25.4%)	94 (19.4%)
Overall allograft failure	234 (23.8%)	74 (33.9%)	82 (35.8%)	144 (25.5%)
DCGL	149 (16.6%)	40 (21.7%)	34 (18.7%)	46 (9.9%)

DWGF, death with functioning graft; DCGL, death-censored graft loss; PTDM/-Meds, transplant recipients with ADA criteria PTDM. PTDM+/Medication: transplant recipients with ADA criteria PTDM and glucose-lowering medication as an outpatient during or at year 1.

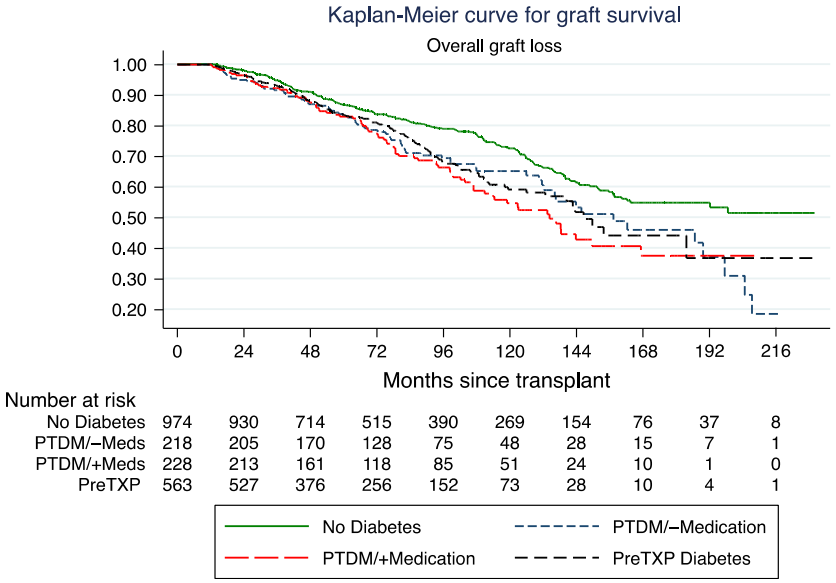

Figure 2 Kaplan–Meier curve for all-cause allograft loss.

1.53, P = 0.269; PTDM/+Meds: HR 1.28, 95% CI 0.97–1.69, P = 0.074).

Kaplan–Meier curves for death-censored allograft failure by diabetes group are shown in Fig. 3. The log-rank test showed no significant differences for either of the PTDM groups or the DM group vs. NoDM. This finding was confirmed in adjusted model using NoDM as the reference (PTDM/-Meds: HR 1.04, 95% CI 0.78–1.51, P = 0.823; PTDM/+Meds: HR 1.23, 95% CI 0.82–1.86, P = 0.304). Rejection, hepatitis C virus infection, low eGFR, African Americans, and younger KTR were associated with a higher risk of death-censored allograft loss in our cohort.

Overall patient survival and death with functioning allograft patient survival (DWFG)

Kaplan–Meier curves for overall survival are shown in Fig. 4. The log-rank test showed a significantly higher all-cause mortality for both PTDM groups and DM compared to NoDM (log-rank P-value <0.001 for all). After adjustment in the multivariate Cox model, PTDM/+Meds remained an independent risk factor for death (HR 1.81, 95% CI 1.36–2.39, P = 0.004). Although the PTDM/-Meds group had a 33% higher rate of death compared to the NoDM group, this finding was not statistically significant (HR 1.33 95% CI 0.96-1.84, P = 0.086). African Americans had a 25% lower rate of death in our cohort; however, this also did not reach conventional levels of significance (HR 0.75, 95% CI 0.56–1.00, P = 0.057).

Kaplan–Meier curves for DWGF are shown in Fig. 5. The log-rank test showed a significantly higher DWFG for both PTDM groups as well as the DM group (log-rank P-value< 0.05 for all) compared to the NoDM group. After adjustment for confounders, PTDM/+Meds was independently associated with shorter patient survival with a functioning allograft (HR 1.59 95% CI

Table 3. Results of the Cox proportional hazards analyses. Hazard ratios > 1 indicate an increased risk of allograft failure or death; hazard ratios < 1 indicate a decreased risk of allograft failure or death. All variables were adjusted for each other including those with $P > 0.05$ (BMI, cold ischemia time, HLA-DR mismatch, Panel reactive antibody status, tacrolimus as starting agent and CMV disease; not shown). Time on dialysis was a categorical variable: no dialysis, ≤ 1 year, > 1 year.

Characteristic	All-cause allograft loss	DCGL	DWFG	All-cause mortality
PTDM/-Meds	1.16 (0.88–1.53)	1.04 (0.78–1.51)	1.29 (0.83–1.99)	1.33 (0.96–1.84)
PTDM/+Meds	1.28 (0.97–1.69)	1.23 (0.82–1.86)	1.59 (1.05–2.38)*	1.81 (1.36–2.39)*
Male gender	1.08 (0.88–1.34)	0.91 (0.69–1.21)	1.32 (.93–1.86)	1.34 (1.06–1.71)*
Age (per decade)	1.05 (.95–1.16)	0.79 (0.69–0.89)***	1.85 (1.56–2.20)***	1.57 (1.40–1.76)***
African American	1.28 (0.98–1.68)	1.70 (1.21–2.40)**	0.94 (0.59–1.47)	0.75 (0.56–1.00)
Rejection during first year	2.48 (1.77–3.48)***	2.46 (1.59–3.79)***	3.80 (2.28–6.35)***	2.52 (1.73–3.66)***
HCV + recipient	1.92 (1.38–2.69)***	1.93 (1.20–3.09)***	2.62 (1.55– 4.44)***	2.28 (1.66–3.14)***
Delayed allograft function	1.08 (0.85–1.37)	1.06 (0.79–1.40)	1.21 (0.60–1.43)	1.11 (0.86–1.43)
Living donor	0.91 (0.64–1.28)	1.08 (0.77–1.45)	0.78 (0.44–1.36)	0.95 (0.66–1.37)
Glomerulonephritis	1.01 (0.81–1.26)	1.09 (0.88–1.51)	0.80 (0.56–1.16)	1.02 (0.76–1.35)
Cardiovascular disease before transplant	1.52 (0.21–1.91)**	1.69 (1.24–2.31)**	1.58 (1.12–2.24)**	1.34 (1.05–1.70)*
Time on dialysis				
>0–≤1	1.04 (0.75–1.45)	1.09 (0.71–1.66)	1.12 (0.65–1.94)	0.93 (0.64–1.34)
>1 year	1.00 (0.74–1.36)	0.93 (0.62–1.40)	1.06 (066–1.72)	1.22 (0.87–1.70)
Transplant year	0.96 (0.93–1.00)	0.95 (0.91–0.99)*	.91 (0.86–0.96)**	0.94 (0.90–0.98)**
eGFR at 6 months	0.98 (0.97–0.99)**	0.99 (0.98–0.99)***	1.00 (0.98–1.00)	0.99 (.99–1.01)
Donor age (per decade)	1.05 (0.98–1.16)	1.04 (0.94–1.15)	1.02 (0.90–1.16)	1.02 (0.97–1.10)

DCGL, death-censored allograft loss; DWFG, death with functioning allograft; PTDM/-Meds, transplant recipients with ADA criteria PTDM. PTDM+/Medication: transplant recipients with ADA criteria PTDM and glucose-lowering medication as an outpatient during or at year 1.

*$P < 0.05$; **$P < 0.01$;***$P < 0.001$.

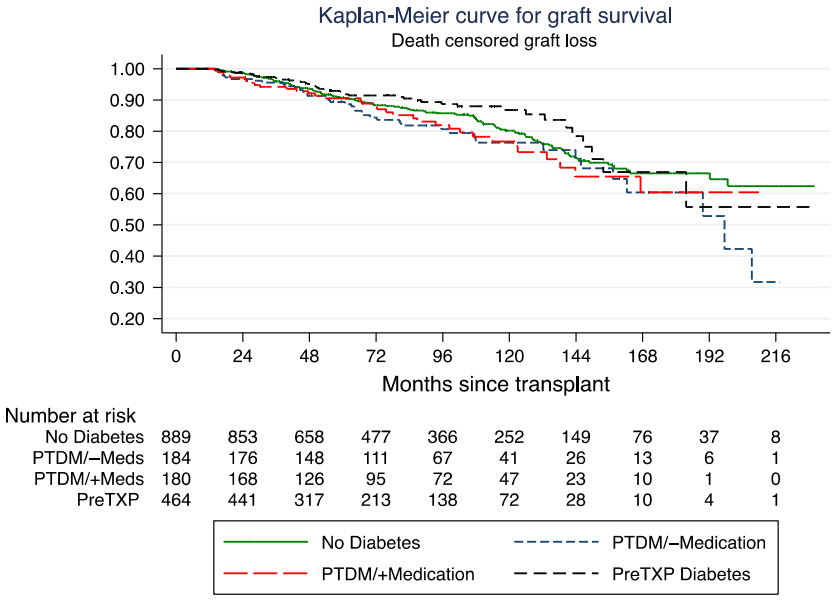

Figure 3 Kaplan–Meier curve for death-censored allograft loss DCGL.

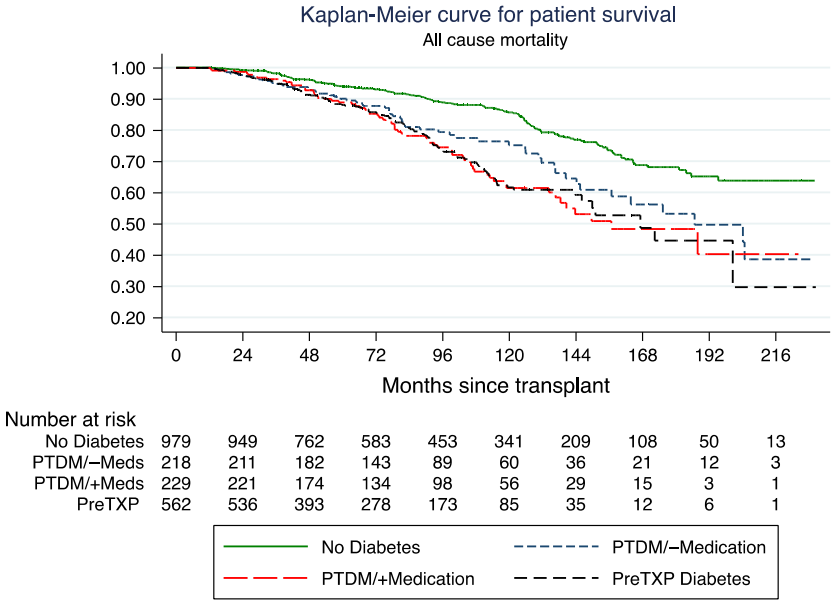

Figure 4 Kaplan–Meier curve for all-cause mortality. The discrepancy in the number of subjects between all-cause mortality and overall allograft loss is due to missing information of graft loss in 7 patients. These patients were therefore censored for the analysis of all-cause graft loss and DCGL.

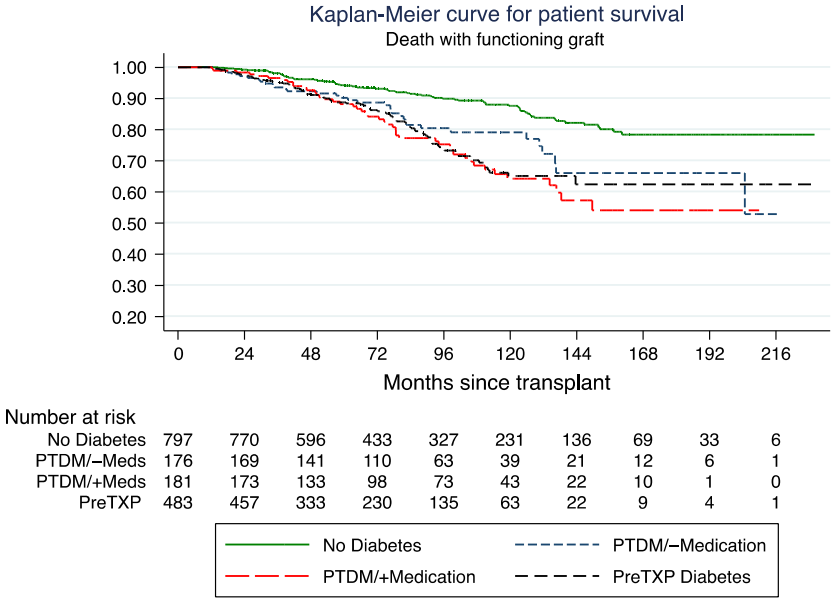

Figure 5 Kaplan–Meier curve for death with functioning allograft (DWFG).

1.05–2.38, $P = 0.025$), and PTDM/-Meds was not (HR 1.29 95% CI 0.83–1.99, $P = 0.248$).

Interaction with time

A hypothesized increase in the relative hazard of death and allograft loss in the PTDM/-Meds and PTDM/+Meds groups over time was explored with different models that included interaction terms with time of follow-up. However, the model without the interaction term showed a better fit than all models examined with an interaction term. Further, the interaction term was not significant in any of the models indicating no detectable change in the relative hazard of death or allograft loss over follow-up time.

Sensitivity analysis

Cox regression analysis comparing the two PTDM groups combined with the NoDM group detected no independent association for overall allograft loss (HR 1.22, 95% CI 0.98–1.52, $P = 0.071$). This finding was likely to have been strongly influenced by the inclusion of deaths because death-censored allograft survival was not associated with PTDM (DCGL HR 0.97, 95% CI 0.86–1.09, $P = 0.634$). PTDM with or without glucose-lowering medications was also an independent risk factor for all-cause mortality (HR 1.46, 95% CI 1.12–1.90; $P = 0.005$) and DWFG (HR 1.44 95% CI 1.02–2.03, $P = 0.035$). A competing risk analysis for allograft loss with death as the competing event was conducted. The results were not significant and similar to the traditional Cox regression analysis (PTDM/-Meds: sHR 1.05, 95% CI 0.71–1.56; PTDM/+Meds: sHR 0.92 95% CI 0.60–1.41). Further, when we excluded the patients from the NoDM group who became diabetic ($n = 22$) after the one year post-transplant, our findings changed minimally (data not shown).

Discussion

In the present study, we evaluated the impact of PTDM on allograft and patient survival in renal transplant recipients. All patients who developed PTDM were diagnosed using ADA criteria; however, they were subdivided into two groups according to prescription of glucose-lowering medication at one year post-transplant. In the multivariable analyses, PTDM requiring glucose-lowering treatment at one year (PTDM/+Meds) was an independent risk factor for all-cause mortality and for death with a functioning allograft. PTDM/+Meds was not an independent predictor for allograft loss or DCGL. These findings from our single-center cohort study provide evidence for important adverse consequences of PTDM in the era of immunosuppressive regimens that predominantly include depleting antibody induction therapy, tacrolimus, mycophenolate, and low-dose prednisone. Tacrolimus was not associated with patient or allograft survival benefit in the present study. In other studies however, despite being more diabetogenic than cyclosporine, tacrolimus has been reported to benefit kidney transplant recipients [17,18]. The failure to detect this association in our study may be due to the relatively small amount of calcineurin inhibitor variation as the vast majority of recipients received tacrolimus.

A detrimental effect of PTDM on patient survival has been previously reported [8,9,14]. However, the three most recently published studies from the United States have not detected independent associations between PTDM and either allograft survival, all-cause mortality, or DWFG [11–13]. It has been speculated that these negative findings may have been due to the enrollment of only patients transplanted after the year 2000 when greater awareness and pro-active treatment of PTDM may have reduced the consequences of this disease (the study by Pirsch *et al.* was a multicenter RCT with relatively low-risk patients and a short follow-up, which led to few outcomes). Small study sample size and brief follow-up time might also have reduced the ability of some prior studies to detect an independent effect of PTDM. A Norwegian study published in 2011 enrolled 1410 patients from 1995 to 2006 with a mean follow-up time of 6.7 years and found a hazard ratio of PTDM for all-cause mortality of 1.54 (95% CI 1.09–2.17) [14]. A prospective single-center study from the same group with a follow-up time of 8 years, but only 201 patients found no association between PTDM and all-cause mortality [19]. Cosio and colleagues included 1811 patients from 1983 to 1997 in a single-center study from the United States with a mean follow-up time of 8.3 years and detected a HR of PTDM on all-cause mortality of 1.8 (95% CI 1.35–2.41). Two registry studies with 4 and 7 years of follow-up using data from the United States Renal Data System (USRDS) with 27 707 enrolled kidney transplant recipients in one and 11 659 in the other showed both increased HR for all-cause mortality among transplant recipients with PTDM (the recruitment periods in these two studies overlapped greatly) [9,20].

Another possible reason for not detecting associations between PTDM and mortality in the recently published studies might have been dilution of the PTDM group with patients experiencing transient diabetes. Yates *et al.* have recently emphasized the need to distinguish reversible/transient PTDM from persistent PTDM [21]. In our study, PTDM/-Meds, which could be interpreted as transient post-transplant diabetes mellitus, was not an independent risk factor for all-cause mortality or DWFG. Although elevations in blood glucose lead to increases in cardiovascular risk outside of the setting of kidney disease [22,23], transient PTDM has not been linked to the same outcomes [24]. One group has investigated the consequences of impaired fasting glucose and impaired glucose tolerance after transplantation and found it to be associated with higher all-cause mortality, but not to elevated cardiovascular mortality [14].

Cosio *et al.* were able to link impaired fasting glucose levels at one, four, or twelve months to cardiovascular events [25]. In our study, reversible PTDM was not independently associated with allograft survival. Although patient survival in the setting of reversible PTDM was lower than in nondiabetics, this finding did not reach conventional levels of statistical significance.

In the present study, PTDM was not independently associated with increased death-censored allograft loss in the PTDM/-Meds or the PTDM/+Meds group. The previously mentioned registry studies were able to show an association of PTDM with allograft loss [9,20]. Yet this association with allograft loss overall was driven by death events. Only, Kasiske *et al.* was also able to demonstrate an independent association with DCGL [9]. However, the investigators did not adjust for rejection and it is likely that many allograft losses were due to rejection (which in turn may have led to PTDM due to high doses of immunosuppressive drugs as anti-rejection therapy).

Only two single-center studies have reported significant associations between PTDM and allograft survival. However, one of these studies only adjusted for gender, age, race, and creatinine at 1 year and the other only provided unadjusted results [5,6]. Taken collectively, these published findings and the results of our study do not strongly support the interpretation that PTDM influences allograft survival.

An outstanding question about PTDM is the duration of time necessary for it to instigate negative health consequences. Although we hypothesized that the influence of PTDM increases over time, we found no evidence for this. There are multiple explanations for this phenomenon. First, it could be that most KTR's have either undiagnosed glucose metabolism impairments prior to transplantation. This is supported by a previous study from our group where we observed that 57% of incident kidney transplant recipients met criteria for metabolic syndrome at the time of transplantation [26]. Moreover, in the present study, the pretransplant cardiovascular disease prevalence was higher in all the groups with deranged glucose metabolism than in nondiabetic patients. This could explain why large registry studies have shown independent effects of PTDM on mortality despite short follow-up time. This in turn could also explain the lack of a significant interaction as PTDM influenced events begin to happen early on after transplantation and therefore "wash out" an interaction with time. Second, PTDM may be a more aggressive type of diabetes that, unlike type 2 DM, has a shorter "incubation period."

Our study has limitations. First, it may have limited generalizability because it represents the experience of a single clinical center. Further, Asian and Hispanic patients comprised a smaller proportion of patients than in nationally representative populations. Finally, we only included patients receiving a first kidney transplant. Despite these limitations, the present study has a large representation of African American recipients and is not limited by possible confounding by prior exposure to immunosuppressive drugs.

Our dataset also lacked the exact dates of onset of PTDM. However, this shortcoming was mitigated by the fact that the majority of cases of PTDM develop within the first few months after transplantation. Patients who were lost to follow-up, who lost their allograft, or who died before 1 year post-transplant were excluded. The classification of groups according to the use of glucose-lowering medication use cannot imply that patients in the PTDM/-Meds group had transient diabetes. However, a misclassification would have let to a bias away from the null.

Subsequent to one year post-transplant, many patients had their laboratory testing done outside of the University of Pennsylvania Health System, necessitating the examination of laboratory values or medication prescriptions to diagnose PTDM. Accordingly, there may have been patients with elevated glucose levels unknown to us, and who had not been prescribed GLM. This would have led to misclassification of such patients with true PTDM as having no PTDM in our analyses. Such misclassification would, most likely, have biased our findings toward the null.

As with any retrospective study, there may be residual confounding after multivariable adjustment. We did not have access to some traditional cardiovascular risk factors such as smoking status, cholesterol levels, or hypertension. Additionally, BK virus was not included in our analysis because it was not assessed uniformly over the follow-up period.

In conclusion, this study, which reflects contemporary practice in the United States in terms of immunosuppression, cardiovascular disease prevention, and management of hyperglycemia, demonstrated the deleterious effects of PTDM among patients requiring glucose-lowering medications one year post-transplant. Further, it demonstrates that transient PTDM has less severe consequences. The elevated rate of death beginning very soon after transplant among our patients with drug-treated PTDM is suggestive of the possibility that it was preceded by undiagnosed pretransplant glucose metabolism disorders or metabolic syndrome that puts

these patients at a higher risk of death very soon after transplantation. More intensive pretransplant screening for DM will clarify how often occult DM exists at the time of transplantation. Finally, in light of the genesis of PTDM being strongly linked to current day immunosuppressive regimens, our findings also suggest that PTDM be an endpoint in clinical trials for new immunosuppressive drugs.

Authorship

TD: Responsible for study design, the acquisition, analysis and interpretation of data. Furthermore, drafting and revision of the manuscript and final approval of the version to be published and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. NF: Substantial contribution to the design of the manuscript, substantial contribution to the revision for intellectual content and final approval of the version to be published. Agrees to be accountable for all aspects of the work. YL: Substantial contribution to the design of the manuscript, substantial contribution to the revision for intellectual content and final approval of the version to be published. Agrees to be accountable for all aspects of the work. SG: Substantial contribution to the acquisition of data for the work and critical revision for intellectual content and final approval of the version to be published. Agrees to be accountable for all aspects of the work. NK: Substantial contribution to the acquisition of data for the work and critical revision for intellectual content and final approval of the version to be published. Agrees to be accountable for all aspects of the work. RDB: Substantial contribution to the design of the manuscript, substantial contribution to the revision for intellectual content and final approval of the version to be published. Agrees to be accountable for all aspects of the work. HIF: Substantial contribution to the conception and design of the manuscript, substantial contribution to the revision for intellectual content and final approval of the version to be published. Agrees to be accountable for all aspects of the work.

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Conflict of interest

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