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Impact of Post-Transplant Diabetes Mellitus on Survival and Cardiovascular Events in Kidney Transplant Recipients

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Background: Post-transplant diabetes mellitus (PTDM) is a risk factor for poor outcomes after kidney transplantation (KT). However, the outcomes of KT have improved recently. Therefore, we investigated whether PTDM is still a risk factor for mortality, major atherosclerotic cardiovascular events (MACEs), and graft failure in KT recipients.

Methods: We studied a retrospective cohort of KT recipients (between 1994 and 2017) at a single tertiary center, and compared the rates of death, MACEs, overall graft failure, and death-censored graft failure after KT between patients with and without PTDM using Kaplan-Meier analysis and a Cox proportional hazard model.

Results: Of 571 KT recipients, 153 (26.8%) were diagnosed with PTDM. The mean follow-up duration was 9.6 years. In the Kaplan-Meier analysis, the PTDM group did not have a significantly increased risk of death or four-point MACE compared with the non-diabetes mellitus group (log-rank test, $P=0.957$ and $P=0.079$, respectively). Multivariate Cox proportional hazard models showed that PTDM did not have a negative impact on death or four-point MACE ($P=0.137$ and $P=0.181$, respectively). In addition, PTDM was not significantly associated with overall or death-censored graft failure. However, patients with a long duration of PTDM had a higher incidence of four-point MACE.

Conclusion: Patient survival and MACEs were comparable between groups with and without PTDM. However, PTDM patients with long duration diabetes were at higher risk of cardiovascular disease.

Keywords: Kidney transplantation; Diabetes mellitus; Cardiovascular diseases; Mortality; Graft survival

INTRODUCTION

Kidney transplantation (KT) is the recommended treatment for selected patients with end-stage renal disease (ESRD), because it improves survival and quality of life compared with long-term dialysis [1]. However, there are many complications related to the surgery and immunosuppressant medications following KT. Post-transplant diabetes mellitus (PTDM), i.e., diabetes newly detected after transplantation, is a common complication (incidence of 10% to 25%) [2-4]. PTDM is associated with a poor prognosis after KT [2,5,6]. This can be explained by the fact that chronic hyperglycemia leads to micro- and macrovascular complications and death. As outcomes of KT, long-term graft and patient survival have recently improved in both deceased

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and living donor KT recipients, despite unfavorable changes in donor and recipient factors [7]. This improved prognosis after KT may be experienced by KT recipients with PTDM.

Some recent studies of patients who underwent KT after 2000 reported no unfavorable impact on clinical outcomes, including coronary artery disease and graft failure [6,8]. Therefore, this study investigated whether PTDM was associated with incident mortality, major atherosclerotic cardiovascular events (MACEs), and graft failure in KT recipients during the last 20 years.

METHODS

Study design

This 27-year observational cohort study of KT recipients was conducted at a single tertiary center in Korea. Subjects were excluded if they had diabetes before KT, were aged <18 years at the time of KT, were lost to follow-up, or had received two or more graft transplantations. The study analyzed 571 of 810 KT recipients who underwent transplantation from 1994 to 2017 and were followed until 2021. The Institutional Review Board of Ajou University Hospital approved the study protocol (AJOUIRB-MDB-2019-145). Informed consent was waived by the board. This study conformed to the guidelines of the Declaration of Helsinki. Medical records were obtained from the institutional electronic database.

The definition of PTDM was based on the American Diabetes Association criteria: fasting plasma glucose ≥126 mg/dL; 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test; or the requirement for glucose-lowering drugs, including oral hypoglycemic agents and insulin injection. The duration of PTDM was calculated starting from the date of diagnosis. The outcome measures were the four-point MACE (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina), all-cause mortality, overall graft failure, and death-censored graft failure rates. Death or the requirement for dialysis due to failed kidney transplant was considered to indicate overall graft failure. Cases requiring dialysis after KT were classified as death-censored graft failure. As a baseline comorbidity, cardiovascular disease (CVD) included a history of coronary heart disease (CHD), cerebrovascular disease, and peripheral arterial disease. The causes of ESRD were determined by a kidney transplant specialist.

Immunosuppressive protocol

Prior to 2001, induction therapy did not always feature administration of anti-thymocyte globulin and an anti-CD3 antibody. The maintenance immunosuppressant combination was cyclosporine, mycophenolate mofetil, and corticosteroids. Since 2001, the immunosuppressive regimen consisted of basiliximab as induction therapy, a calcineurin inhibitor (tacrolimus or cyclosporine), mycophenolate mofetil, and corticosteroids. High-dose glucocorticoids were administered intravenously for several days after transplantation and the dose was reduced gradually. When acute rejection was suspected and confirmed by liver biopsy, high-dose glucocorticoid was given and then tapered.

Statistical analyses

All statistical tests were performed using SPSS software version 19.0 (IBM Co., Armonk, NY, USA) or R version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are expressed as means±standard deviations or medians with interquartile ranges, and were compared between two groups using Student's *t* test and the Mann-Whitney *U* test. Categorical variables are presented as numbers and percentages and were assessed using the chi-square test or Fisher's exact test. Kaplan-Meier curves were used to analyze four-point MACE and all-cause death, and the log-rank test was used to compare the curves. Multivariate-adjusted hazard ratios (HRs) for kidney transplant outcomes, such as four-point MACE, all-cause death, overall graft failure, and death-censored graft failure, were analyzed using Cox proportional hazard models. The assumptions for the Cox proportional hazards model were examined with the Schoenfeld test (1980), i.e., whether the Schoenfeld residuals scattered randomly around zero after regressing those for each time *t* was determined. For a model violating the assumptions, a "time-dependent" proportional hazards model was constructed by adding time-dependent covariates (Supplemental Fig. S1). Two-sided *P* values <0.05 were considered statistically significant.

RESULTS

Characteristics of the PTDM and non-PTDM groups

The study population was followed for a mean of 9.6 years. At the time of KT, the mean age of the subjects was 43.6 years and 69.4% had hypertension as a comorbidity (n=396). The main causes of ESRD were glomerulonephritis (21.5%), polycystic kidney disease (3.9%), and hypertension (3.7%) (Table 1). FK506 (60.2%) was the calcineurin inhibitor used most after KT, followed by cyclosporine (39.8%). Half of the subjects received a kidney from a living donor (51.3%) (Table 1). The KT recipients who developed PTDM were older and more likely to be obese, smoke, and have hypertension, but did not differ in

Table 1. Patient Baseline Characteristics according to Post-Transplant Diabetes Status

Characteristic	No PTDM (n=418)	PTDM (n=153)	P value
Age, yr	42.6±10.4	46.4±9.0	<0.001
Male sex	236 (56.5)	82 (53.6)	0.569
BMI, kg/m^2	21.8 (20–24)	23.0 (21–25)	<0.001
Glucose, mg/dL[a]	93.3±12.2	96.5±12.4	0.007
HbA1c, %[b]	5.16±0.42	5.30±0.54	0.023
Type of dialysis			
Peritoneal dialysis	67 (16.0)	24 (15.7)	0.936
Hemodialysis	347 (83.0)	128 (83.7)	
Preemptive	4 (1.0)	1 (0.7)	
Smoking	22 (13.2)	48 (31.4)	<0.001
Comorbidities			
HTN	271 (64.8)	125 (81.7)	<0.001
CVD	12 (2.9)	6 (3.9)	0.589
Waiting time, mo	35.7 (5–70)	34.5 (3–66)	0.708
Immunosuppressive drugs			
Tacrolimus	242 (57.9)	102 (66.7)	0.067
Cyclosporine A	176 (42.1)	51 (33.3)	
Cause of ESRD			
GN[c]	103 (24.6)	20 (13.1)	0.049
Hypertension	15 (3.6)	6 (3.9)	
Lupus	7 (1.7)	4 (2.6)	
PCKD	13 (3.1)	9 (5.9)	
Miscellaneous[d]	5 (1.2)	1 (0.7)	
Unknown	275 (65.8)	113 (73.9)	
Donor characteristics			
Age, yr	42.7 (31–52)	43.4 (30–51)	0.893
Male sex	249 (59.6)	62 (40.5)	0.999
ABO incompatible	7 (1.7)	3 (2.0)	0.730
Living	208 (49.9)	85 (56.3)	0.185
Transplant era			
1994–2007	116 (27.8)	46 (30.1)	0.601
2008–2017	302 (76.5)	107 (69.9)	

Values are expressed as mean±standard deviation, number (%), or median (interquartile range).
PTDM, post-transplant diabetes mellitus; BMI, body mass index; HbA1c, hemoglobin A1c; HTN, hypertension; CVD, cardiovascular disease; ESRD, end-stage renal disease; GN, glomerulonephritis; PCKD, polycystic kidney disease.
[a]Includes random or fasting blood glucose levels measured in 565 subjects of the total of 571; [b]From 337 subjects of the total of 571; [c]Includes immunoglobulin A nephropathy, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, and membranous glomerulonephritis; [d]Includes Alport syndrome, interstitial nephritis, pyelonephritis, and post-streptococcal glomerulonephritis.

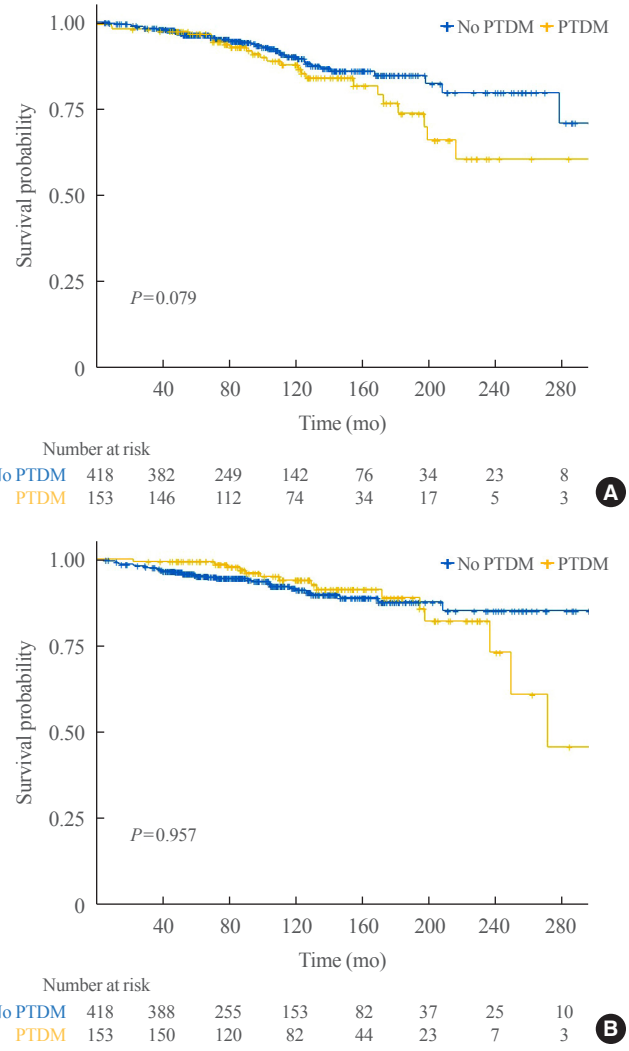

Fig. 1. Kaplan-Meier curves for all-cause mortality and four-point major adverse cardiovascular events according to post-transplant diabetes mellitus (PTDM) status (log-rank test, P=0.957 and P=0.079, respectively). (A) All-cause mortality. (B) Four-point major adverse cardiovascular events.

terms of donor characteristics from KT recipients who did not develop PTDM (Table 1). The cumulative incidence of PTDM was similar between the two transplant periods (1994 to 2007, 28%; 2008 to 2017, 26%).

Comparison of KT outcomes between the PTDM and non-PTDM groups

During follow-up, 153 (26.8%) KT recipients were diagnosed with PTDM, 64 (11.2%) had four-point MACE, and 48 (8.4%) died. The main causes of death were infectious disease (n=18; 37.5% of deaths), CVD (n=15; 31.3%), and cancer (n=5; 10.4%).

Table 2. Multivariate Analysis of All-Cause Mortality and Four-Point Major Adverse Cardiovascular Events

Variable	Hazard ratio	95% CI		*P* value
		Lower	Upper	
All-cause mortality[a]				
Age (per year increase)	1.064	1.027	1.102	<0.001
Female sex	1.881	0.948	3.733	0.071
Smoker	2.330	0.964	5.631	0.060
BMI, kg/m^2 (per 1 kg/m^2 increase)	1.055	0.946	1.177	0.338
Hypertension	2.002	0.683	5.870	0.206
History of cardiovascular disease	1.175	0.268	5.150	0.831
2008–2017 transplant era (vs. 1994–2007)	0.351	0.165	0.747	0.007
Donor age	1.012	0.988	1.036	0.343
Deceased donor (vs. living donor)	1.830	0.950	3.523	0.071
PTDM	3.722	0.658	21.042	0.137
Duration of PTDM	1.239	0.933	1.646	0.139
Four-point major adverse cardiovascular events[b]				
Age (per year increase)	1.048	1.016	1.081	0.003
Female sex	0.902	0.492	1.654	0.738
Smoker	2.247	1.150	4.389	0.018
BMI, kg/m^2 (per 1 kg/m^2 increase)	1.050	0.949	1.163	0.344
Hypertension	1.411	0.765	2.603	0.271
History of cardiovascular disease	5.091	2.255	11.494	<0.001
2008–2017 transplant era (vs. 1994–2007)	0.566	0.293	1.094	0.090
Donor age	1.009	0.989	1.029	0.370
Deceased donor (vs. living donor)	3.412	1.838	6.335	<0.001
PTDM	0.600	0.284	1.268	0.181
Duration of PTDM	1.101	1.024	1.183	0.009

CI, confidence interval; BMI, body mass index; PTDM, post-transplant diabetes mellitus.
[a]Time-varying covariate: hypertension, PTDM, duration of PTDM; [b]There are no time-dependent covariates because all variables satisfy the proportional hazard assumptions.

Regarding the Kaplan-Meier curves (Fig. 1), the PTDM group did not have poorer in terms of all-cause death or four-point MACE (P=0.957 and P=0.079, respectively), although they exhibited a higher risk trend for MACE. To identify risk factors for MACEs and all-cause death, a Cox proportional hazard model was constructed including the duration of PTDM and variables affecting KT outcomes, according to the Kaplan-Meier curves of all-cause death and four-point MACE for both groups (which began to diverge as follow-up progressed). Older age was positively associated with a higher risk of all-cause death (HR, 1.06; P<0.001) and transplantation from 2008 to 2017 with a lower risk of all-cause death (HR, 0.35; P=0.007) (Table 2). Old age (HR, 1.05; P=0.003), history of smoking (HR, 2.25; P=0.018), CVD (HR, 5.09; P<0.001), and transplantation from a deceased donor (HR, 3.41; P<0.001) were all associated with a high risk of four-point MACE (Table 2). PTDM was not a risk factor for all-cause death (HR, 3.72; P=0.137), four-point MACE (HR, 0.60; P=0.181), overall graft failure (HR, 2.33; P=0.054), or death-censored graft failure (HR, 2.11; P=0.140) (Tables 2, 3). However, a long duration of PTDM was associated with a higher risk of four-point MACE (HR, 1.10; P=0.009) (Table 2).

DISCUSSION

This study followed 571 KT recipients at a single tertiary center over 27 years. PTDM was not a significant risk factor for major adverse outcomes of KT recipients, such as all-cause death and

Table 3. Multivariate Analysis of Overall and Death-Censored Graft Failure

Variable	Hazard ratio	95% CI		*P* value
		Lower	Upper	
Overall graft failure[a]				
Age (per year increase)	0.990	0.970	1.009	0.290
Female sex	1.335	0.912	1.957	0.138
Smoker	1.546	0.951	2.516	0.079
BMI, kg/m^2 (per 1 kg/m^2 increase)	1.053	0.988	1.123	0.113
Hypertension	1.655	0.888	3.084	0.113
History of cardiovascular disease	2.041	0.923	4.513	0.078
2008–2017 transplant era (vs. 1994–2007)	0.640	0.415	0.988	0.044
Donor age	1.028	1.014	1.043	<0.001
Deceased donor (vs. living donor)	1.480	1.008	2.173	0.046
PTDM	2.331	0.945	5.520	0.054
Duration of PTDM	1.121	0.985	1.276	0.084
Death-censored graft failure[b]				
Age (per year increase)	0.965	0.944	0.987	0.002
Female sex	1.195	0.762	1.874	0.439
Smoker	1.566	0.905	2.710	0.109
BMI, kg/m^2 (per 1 kg/m^2 increase)	1.053	0.977	1.134	0.177
Hypertension	1.798	1.110	2.914	0.017
History of cardiovascular	2.686	1.124	6.422	0.026
2008–2017 transplant era (vs. 1994–2007)	0.754	0.455	1.249	0.273
Donor age	1.034	1.017	1.051	<0.001
Deceased donor (vs. living donor)	1.436	0.915	2.253	0.116
PTDM	2.109	0.783	5.684	0.140
Duration of PTDM	1.111	0.961	1.285	0.154

CI, confidence interval; BMI, body mass index; PTDM, post-transplant diabetes mellitus.
[a]Time-varying covariates: hypertension, PTDM, and duration of PTDM; [b]Time-varying covariates: PTDM, duration of PTDM.

four-point MACE. In addition, PTDM was not strongly associated with increased long-term graft loss, such as overall and death-censored graft failure. However, long duration PTDM was a potential risk factor for four-point MACE. The cumulative incidence of PTDM was 26.8% (153/571) during the 10-year follow-up period. Subjects who developed PTDM were older and more likely to be obese, smokers, and hypertensive, similar to patients with pretransplant DM. The incidence of PTDM did not differ significantly according to transplant era.

Although KT reduces the risk of CVD and mortality compared with remaining on the transplant waiting list, KT recipients still have higher CVD and mortality risks than the general population [9]. In this study, the risk factors for all-cause mortality were old age and early, rather than recent, KT. Despite the KT recipients being older and having more comorbidities, improved management of KT recipients with comorbidities and advanced perioperative care and surgical techniques have improved the KT success and survival rates. In one long follow-up study, the survival of KT recipients improved by 20% compared with 10 years earlier [10]. In an analysis of Korean data, the 1-year mortality rate after KT showed improvement over time [11]. In the present study, factors associated with an increased risk of CVD in KT recipients were old age, smoking, prior CVD, transplantation from a deceased donor, and long duration PTDM. Old age, smoking, and prior CVD are traditional risk factors for four-point MACE in KT recipients, as in the general population [12]. Transplantation from deceased donors is a risk factor for post-transplant myocardial infarction in KT patients [13].

The effect of PTDM on the development of CVD and death remains unclear. Numerous studies have reported negative effects of PTDM on CVD and mortality [14,15]. However, the risk posed by PTDM for poor clinical KT outcomes may have decreased relative to previous studies [6,16]. As the outcomes of diabetes have recently improved; appropriate treatment of PTDM and strict management of other risk factors may be a contributing factor. In addition, the studies differ in terms of the KT populations, study designs, immunosuppression regimens, follow-up durations, transplantation eras, and race.

Regarding the Kaplan-Meier curves for four-point MACE in this study, the curves began to diverge between the two groups after prolonged follow-up. The duration of diabetes is the most important factor when assessing CVD risk in patients with this comorbidity. The European Society of Cardiology and European Association for the Study of Diabetes used the duration of diabetes as a criterion for risk stratification of CVD in patients with diabetes [17]. Patients with diabetes for ≥10 years were at higher risk of CVD than those with diabetes for <10 years. The CHD risk in patients with diabetes increased significantly with diabetes duration, and long duration diabetes was strongly associated with a higher risk of coronary artery events [18,19]. Specifically, a long duration of diabetes, rather than diabetes itself, was suggested as a risk factor for coronary artery disease [18]. The association between diabetes duration and elevated CHD risk could be explained by longer exposure to chronic hyperglycemia. Gaynor et al. [6] suggested that the time taken for PTDM to negatively influence KT outcomes is considerable. In this context, we reported, in a cohort study, that pretransplant diabetes, which implies a longer exposure to chronic hyperglycemia than PTDM, was a risk factor for four-point MACE and post-transplant mortality [4]. The present study suggests that PTDM patients with long duration diabetes have a significantly elevated risk of CVD.

Unlike four-point MACE, long duration PTDM was not risk factor for all-cause mortality. The time taken for PTDM to negatively impact mortality may be longer compared with four-point MACE. In our study, the Kaplan-Meier curves of all-cause mortality diverged between the two groups later than that of four-point MACE. In addition, unlike Western populations, in this study, cardiovascular death represented a small proportion of deaths after KT. The death rate was also lower than that of four-point MACE.

The purpose of this study was to investigate the effect of PTDM on the outcomes of KT, such as four-point MACE, death after KT, and graft failure, using data from a long-term, single-center follow-up study of Korean patients who underwent KT using a standard protocol. This study had several limitations. First it was a single-center retrospective cohort study, and may not represent the general transplant recipient population. Moreover, the incidence of events was low because the number of subjects was relatively small, although they were followed for a long period. It is necessary to collect more data and perform a large, multicenter prospective study. Second, we focused on Korean kidney recipients, so our findings might not be generalizable to other populations and ethnic groups.

In summary, this long-term follow-up cohort study provided no evidence that PTDM is a risk factor for four-point MACE and mortality in KT recipients. The negative effects of PTDM have been reduced through close monitoring of PTDM onset, and proper management of the disease and related risk factors (hypertension and dyslipidemia). However, long duration PTDM, rather than simply the disease itself, was associated with an increased risk of four-point MACE. Since the complications of diabetes, such as four-point MACE, are associated with prolonged exposure to hyperglycemia, close attention and appropriate management are required for glycemic control of KT recipients with PTDM.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: J.Y.J., S.J.H. Acquisition, analysis, or interpretation of data: J.Y.J., S.H.B., B.H.P., S.J.H. Drafting the work or revising: J.Y.J., N.L., H.J.K., D.J.K., K.W.L., S.J.H. Final approval of the manuscript: J.Y.J., S.H.B., B.H.P., N.L., H.J.K., D.J.K., K.W.L., S.J.H.

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