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Patient survival after renal transplantation: IV. Impact of post-transplant diabetes

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Patient survival after renal transplantation: IV. Impact of post-transplant diabetes.

Background. The development of de novo diabetes mellitus is a serious complication of kidney transplantation. This study examined the cardiovascular risk profile of patients with post-transplant diabetes (PTDM) and assessed the impact of PTDM on patient survival.

Methods. This analysis included 1811 adult, renal allograft recipients, transplanted in a single institution between 1983 and 1998. Patient survival was analyzed by univariable and multivariable Cox regression considering PTDM as a time dependent variable.

Results. After a follow-up period of 8.3 ± 4.5 years, 293 patients (20%) developed PTDM, 14% lost their graft, and 20% died. Compared to patients without DM (NoDM, $N = 1186$) patients with PTDM were significantly older (40 ± 14 vs. 48 ± 12 years, $P < 0.001$), heavier (76 ± 23 vs. 86 ± 25 kg, $P < 0.001$), and included more African Americans (18 vs. 28%, $P = 0.001$). In addition, the incidence of PTDM was significantly higher in patients who were transplanted after 1995 than prior to that year. In contrast, there were no significant differences between PTDM and patients who had DM before the transplant (DM; $N = 332$). Compared to NoDM, patients with PTDM had significantly higher total serum cholesterol and triglycerides (TG), higher systolic blood pressure and higher pulse pressure throughout the post-transplant period. Of interest, all of these abnormalities preceded the development of PTDM. Hypertriglyceridemia was particularly pronounced in PTDM and elevated TG levels correlated with the subsequent development of PTDM, independent of other risk factors ($P = 0.001$ by multivariate Cox). Compared to NoDM (16% mortality) a significantly higher percent of DM (31%, $P < 0.001$) and PTDM (22%, $P = 0.005$) patients died. By Cox regression, PTDM correlated with reduced patient survival (hazard ratio = 1.80, CI 1.35 to 2.41, $P = 0.001$), and that relationship was independent of other correlates of reduced survival that included: increasing age; transplant year; reduced serum albumin; and male sex.

Conclusions: PTDM is associated with an unfavorable cardiovascular risk profile that precedes the development of hyperglycemia. PTDM is an independent predictor of reduced survival in renal allograft recipients.

Key words: transplantation, kidney, diabetes, survival, cardiovascular risk.

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Over the last three decades considerable improvements have been made in the survival of renal allografts [1] and of their recipients [2]. Still, compared to the general population, the survival of recipients of kidney transplants is significantly reduced [3]. This observation may not be unexpected because patients with kidney disease, when they reach the final stages of the disease, already have an unfavorable cardiovascular risk profile [4]. Recent studies showed that the cardiovascular risk factors that are relevant to the general public are also relevant to patients with kidney transplants [5]. In previous studies we initiated a systematic evaluation of variables that correlate with the survival of kidney transplant recipients. Those studies led us first to the demonstration that dialysis prior to transplantation has a negative impact on patient survival after transplantation [6] and also that smoking has a profound negative impact on the survival of transplanted patients [7]. Our more recent studies reported on variables that predispose patients to the development of post-transplant diabetes (PTDM) and found that the incidence of PTDM has increased sharply since 1995 [8]. Our current follow-up study assessed the possible impact of PTDM on cardiovascular risk and on patient survival after transplantation.

Post-transplant diabetes mellitus is thought to be the consequence of the development of insulin resistance after transplantation [reviewed in 9, 10]. It is also possible, and perhaps more likely, that patients who develop PTDM have insulin resistance prior to the transplant and that this condition is aggravated by the immunosuppressive medications used after transplantation, among other factors. This postulate is supported by the observations that the patient's characteristics prior to the transplant predispose to PTDM and that in many cases PTDM

Table 1. Characteristics of the patient population

Patient characteristic	All	NoDM	DM	PTDM
Number of patients	1811	1186	332	293
Age *years*	42.9 ± 14	40 ± 14	47.5 ± 12[a]	48 ± 12[a]
Gender *% males*	59%	58%	60%	63%
Race *% African American*	21%	18.3%	24%[b]	28%[b]
Weight at transplant *kg*	78.8 ± 25	75.6 ± 23	84 ± 30[a]	86 ± 25[a]
BMI[c]	27 ± 7.5	25.9 ± 6.5	29 ± 9.6[a]	29 ± 7[a]

[a] $P < 0.001$ by ANOVA compared to NoDM
[b] $P = .001$ by Chi square compared to NoDM
[c] BMI, body mass index = weight (kg)/height $(m)^2$

develops within the first few weeks after transplantation [8–10]. If indeed patients with PTDM had insulin resistance for a period of time prior to the development of DM, then we need to consider that the accelerated development of cardiovascular disease likely started at the time of initiation of insulin resistance, prior to the development of hyperglycemia, because insulin resistance itself is associated with an increased cardiovascular risk [11].

Insulin resistance is associated with complex metabolic and hemodynamic abnormalities, including [11, 12] truncal obesity; hypertension; dyslipidemia; elevated procoagulant factors [13]; and elevated insulin levels. Several factors may cause—or worsen—insulin resistance in renal allograft recipients, including: (*1*) renal insufficiency [14, 15]; (*2*) the effects of corticosteroids and calcineurin inhibitors [reviewed in 9, 16]; and (*3*) the frequent development of obesity after transplantation [17]. In this study we assessed several of the features of the insulin resistance syndrome in renal transplant recipients.

METHODS

Patient population

The study population included 1811 patients who received their first kidney transplants at The Ohio State University between 1983 and December 1997, and who maintained graft function for at least six months post-transplant. The mean follow-up for the population was 8.3 ± 4.5 years. These patients were subdivided into three groups: (*1*) patients without diabetes before and after the transplant (NoDM, $N = 1186$, 66%); (*2*) patients who had diabetes prior to the transplant (DM, $N = 332$, 18%); and (*3*) patients who developed de novo DM after the transplant (PTDM, $N = 293$; 20%). PTDM was diagnosed when transplanted patients who previously were not diabetic required treatment of hyperglycemia with either oral hypoglycemic agents and/or insulin. One hundred and twenty-eight patients met these criteria but were not included in the PTDM group, because a review of these charts revealed that these patients were hyperglycemic even at the time of transplantation although they were not taking hypoglycemic drugs. Table 1 displays the characteristics of the patient population. Details related to the development of PTDM were reported in a previous publication [8].

All patients received induction immunosuppression during the first few days after receiving the allograft. The induction agent has evolved over the years from Minnesota ALG, to monoclonal antilymphocyte antibodies (OKT3; Ortho Biotech, Raritan, NJ, USA) and in the most recent past to monoclonal anti-CD25 antibodies (Basilxilimab, Simulect; Novartis, Basle, Switzerland). Initiation of cyclosporine treatment post-transplant was delayed until the serum creatinine was ≤2.5 mg /dL. In mid 1995 all patients were started on cyclosporine microemulsion (Neoral) rather than Sandimmune. Furthermore, most patients who were on Sandimmune prior to that time were switched to Neoral. Prior to 1995 most patients received azathioprine (Imuran) in addition to cyclosporine. However, since 1995 all patients received mycophenolate mofetil (CellCept) instead of azathioprine as part of a triple immunosuppression protocol that also included Neoral and prednisone. None of the patients included in this study were treated with FK506 (Prograf) or with sirolimus (Rapamycin).

Clinical data were obtained mainly from an electronic database that contains all of the clinical and laboratory information in our patients. In the majority of patients, only the levels of total serum cholesterol and triglycerides (TG) were obtained routinely. Thus, data on low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol were not analyzed in this study. Serum albumin values were analyzed as the average serum concentration from months 6 to 18 post-transplant. Blood pressures (BP) were measured by the patient at home and reported to the post-transplant office. BP determinations made during outpatient clinic visits were also included in the analysis. Mean arterial pressure (MAP) was calculated as [(systolic BP − diastolic BP)/3) + diastolic BP]. Pulse pressure (PP) was calculated as systolic BP − diastolic BP.

Statistical analysis

Data in the manuscript are expressed as means ± standard deviation of the mean unless indicated otherwise. Proportions were compared by Chi square analysis. Mean values in two groups were compared by the Student *t* test or by a non-parametric test if the data were not normally distributed. Mean values in more than two groups were compared by analysis of variance (ANOVA) or by the Mann-Whitney test if the data were not normally distributed. Patient survival was analyzed by both univariate and multivariate Cox regression and displayed in Kaplan-Meier plots. Patient survival was censored at the time of graft loss. The correlation between PTDM and patient survival was analyzed by Cox regression where PTDM was considered a time dependent variable,

because this complication started at different times following the transplant. To assure that the Cox models were correctly interpreted, the assumption of proportional hazards was formally tested.

RESULTS

Demographic characteristics of the patient population

Table 1 displays the overall characteristics of the patient population and the characteristics of each of the patient groups. As can be seen, and as shown previously [8], compared to the NoDM group, patients who developed PTDM were significantly older, significantly heavier, and included a significantly higher percent of recipients of African American race. In contrast, there were no significant differences between PTDM and DM patients in any of these characteristics (Table 1). As shown previously the incidence of PTDM also correlated with the year of transplant. Thus, PTDM developed more frequently in patients transplanted since 1995 than before that year [8]. Additional comparisons between these patient groups have been reported previously [8].

After a period of follow-up of 8.3 ± 4.5 years 20% of the patients died and 14% lost their grafts for reasons other than patient death. Throughout the post-transplant period 293 out of 1479 patients who were not diabetic before the transplant developed PTDM (20%).

Dyslipidemia

Figure 1 displays average yearly total serum cholesterol and serum TG concentrations post-transplant in NoDM, DM and PTDM patient groups. It should be noted that these data include only values obtained from patients who were followed for the entire period of time shown in the figure, that is, six years. As can be seen in Figure 1A, the concentration of total serum cholesterol increased significantly during the first year post-transplant in all groups of patients. Thereafter, serum cholesterol levels declined progressively in all patient groups. Compared to NoDM, cholesterol concentrations were significantly higher in PTDM at years one, two and three ($P \leq 0.01$, Kruskall-Wallis). In contrast, cholesterol values were not significantly different in PTDM and in DM. Serum TG levels (Fig. 1B) were significantly higher in PTDM than in NoDM throughout the post-transplant period ($P < 0.0001$ on years 0 to 4; $P < 0.01$ on years 5 and 6, Kruskall-Wallis). Serum TG in patients with DM were generally lower than those of PTDM and higher than those in NoDM. These differences in lipid levels were not caused by differences in the frequency of use of lipid lowering agents. In fact, these drugs were used significantly more commonly in patients with PTDM (53% of patients) than in DM (31%) or in NoDM (28%) ($P < 0.001$ by Chi square).

In patients with PTDM, hypertriglyceridemia preceded the development of diabetes. This is shown in Figure 2 where serum TG levels are displayed in two groups of patients: NoDM and PTDM before they developed diabetes. As can be seen, compared to patients with NoDM, serum TG levels were significantly higher, at years 1 through 4, in PTDM. After the fourth year, the numbers of patients in the PTDM group was small ($N < 50$) and thus this analysis was not done on later years.

Because hypertriglyceridemia preceded the development of PTDM, we next examined whether serum TG levels correlated with the development of PTDM. The results of a multivariate analysis, including other variables shown previously to correlate with the development of PTDM [8] are shown in Table 2. As can be seen, elevated serum TG levels correlate significantly with a higher incidence of PTDM and that correlation was independent of other variables, including increasing age; in-

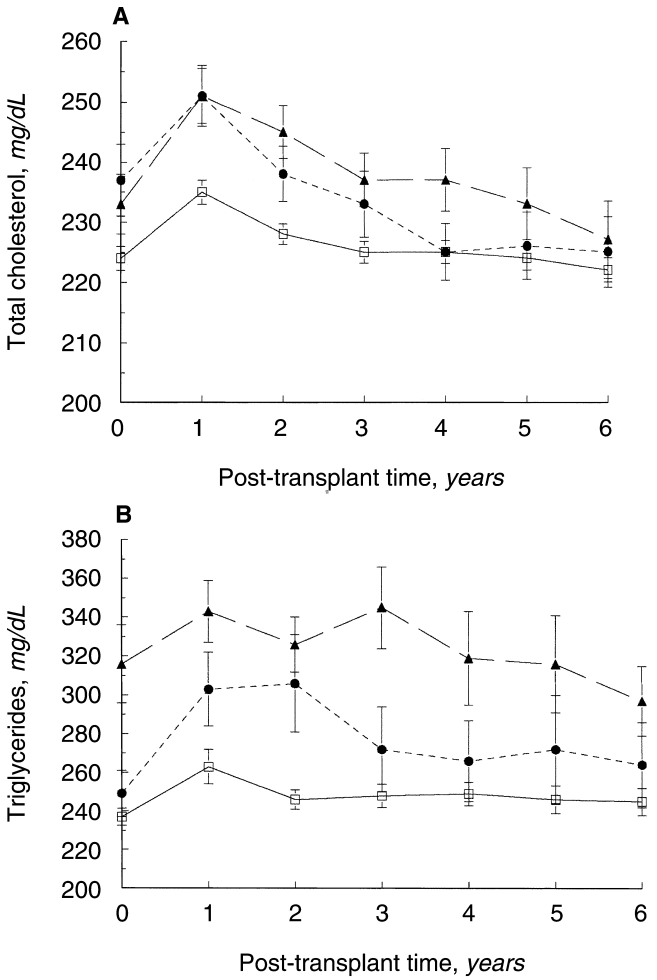

Fig. 1. Evolution of serum lipids concentrations the first six years after kidney transplantation. (*A*) Total serum cholesterol levels (mean ± SEM) in the following groups of patients: no diabetes (NoDM; □—□); with diabetes (DM; ●. . .●); post-transplant diabetes (PTDM; ▲—▲). (*B*) Serum triglyceride (TG) levels (mean ± SEM) in the same groups of patients.

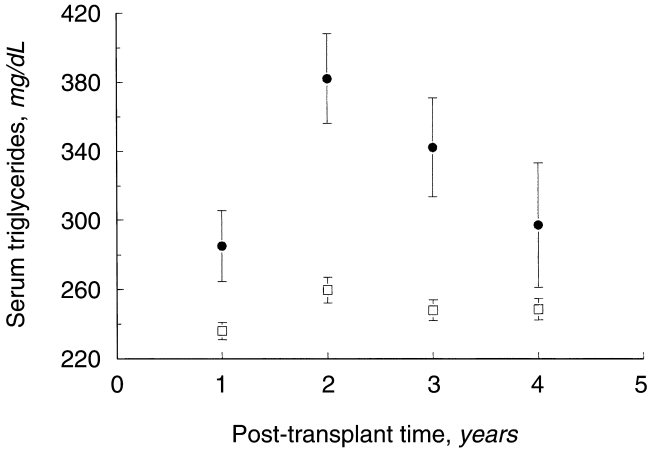

Fig. 2. Serum TG levels in NoDM (□) and PTDM (●) patients before they became diabetic. Data are mean ± SEM. Values represent means and standard errors of the mean. By Wilcoxon: year 1, $P = 0.015$; years 2 and 3, $P < 0.0001$; year 4, $P = 0.001$.

Table 2. Correlates of the development of PTDM (Cox multivariate analysis)

Parameter	RR[a]	*P*
Age *years*	1.33	<0.0001
Race	1.45	0.01
Weight[b] *kg*	1.09	0.01
Year of transplant[c]	1.83	<0.0001
TG *mg/dL*	1.01	0.001

[a] RR = relative risk that was calculated for every 10 years of age, or every 10 kg of weight or every 10 mg/dL increase in serum TG levels

[b] Weight was included in this analysis, rather than the BMI, because the dataset is more complete for this parameter than for BMI values

[c] Patients in this study were transplanted between 1983 and 1998; the incidence of PTDM has increased significantly in recent years, particularly since 1995 [8]

creasing weight; African American race; and more recent transplant year. Regarding the latter variable, we showed previously that, compared to patients transplanted prior to 1995, the incidence of PTDM after that year increased significantly [8]. The correlation between serum TG levels and PTDM was such that 22% of the transplant recipients with serum TG levels <250 mg/dL developed PTDM compared to 28% in patients TG levels between 250 and 600 mg/dL and 36% of the patients with TG ≥ 600 mg/dL ($P = 0.02$ by χ^2 analysis).

Blood pressure levels

Figure 3 displays the evolution of average yearly BP values throughout the post-transplant. As can be seen in Figure 3A, the systolic BP declined sharply during the first year post-transplant in all three groups of patients, and thereafter it remained relatively unchanged. The systolic BP was not significantly different in PTDM and DM. However, these two groups of patients had higher systolic BP than NoDM at all time points ($P < 0.0001$ by ANOVA except years 4 and 5, $P < 0.002$). Figure 3B displays the evolution of the diastolic BP in the three groups of patients. This parameter did not differ significantly between the NoDM and the PTDM groups. However, it is notable that patients in the DM group had significantly lower diastolic BP than the other two groups of patients, except on years 5 and 6 post-transplant ($P < 0.0001$, ANOVA). Finally, Figure 3C displays the evolution of the pulse pressure. Compared to NoDM, pulse pressure was significantly higher in DM and in PTDM at all time points ($P < 0.0001$, ANOVA). A comparison

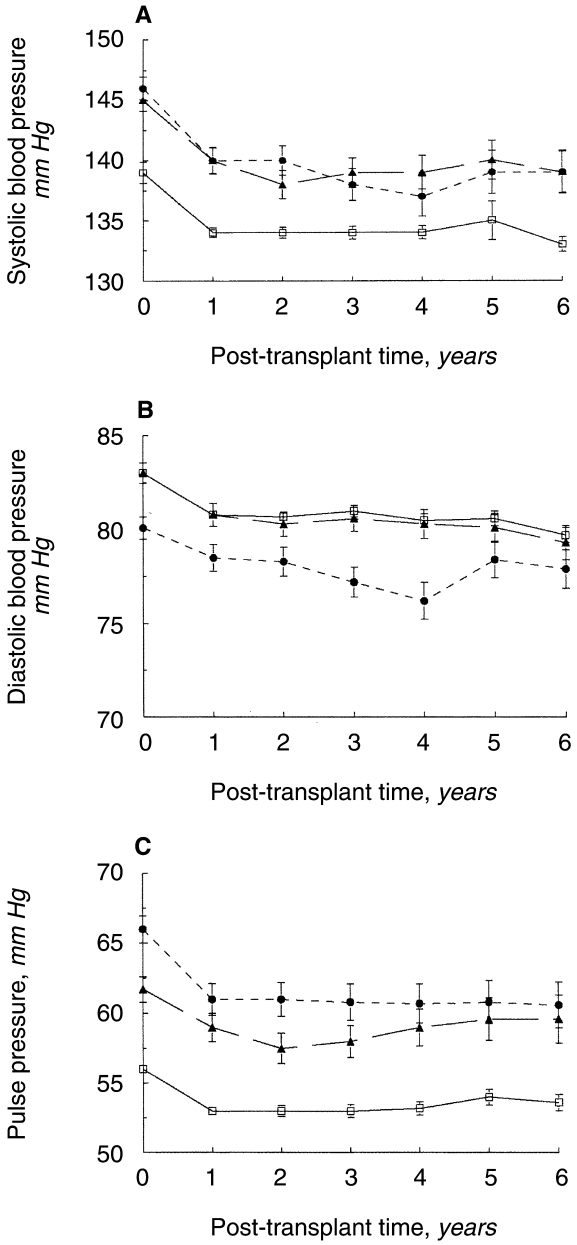

Fig. 3. Changes in blood pressure (BP) levels during the first six years after kidney transplantation. (*A*) Systolic BP, (*B*) diastolic BP, and (*C*) pulse pressure in the three groups of patients, NoDM (□——□), DM (●. . .●) and PTDM (▲——▲). Data are mean ± SEM.

between the pulse pressure values in patients in the DM and PTDM groups revealed the following findings: The pulse pressure was significantly lower in PTDM than in DM at years 0 ($P < 0.0001$) and two ($P = 0.01$). However, after year two the pulse pressure rose progressively in patients with PTDM and it became not significantly different than the pulse pressure of patients with DM.

The BP changes observed in patients with PTDM preceded the development of diabetes. Thus, at one year post-transplant the systolic BP was significantly higher in patients who later developed PTDM than in NoDM (143 ± 13 vs. 139 ± 13 mm Hg, $P = 0.002$) and that difference persisted at two years (137 ± 14 vs. 133 ± 14, $P = 0.006$). Significant differences were also observed on the pulse pressure in years one and two post-transplant (data not shown).

Patient survival

During the follow up period, 16% of NoDM patients died compared to 31% of DM ($P < 0.0001$ by χ^2) and 22% of PTDM ($P = 0.01$). The cause of death was known in approximately 50% of the patients in each group. Compared to NoDM, patients with DM had a significantly higher percent of cardiovascular deaths (49 vs. 69%, $P = 0.02$). However, the number of cardiovascular deaths was not significantly different in NoDM (49%) and PTDM (54%). The degree of glucose control, measured as the average HbA1c during the follow-up period, did not correlate with mortality in either DM or PTDM patients (data not shown).

Figure 4 displays Kaplan-Meier patient survival plots in the three groups of patients. The first analysis plotted patient survival from the date of the transplant (Fig. 4A). As can be seen, survival was significantly worse in DM than in either NoDM or PTDM (log rank $P < 0.0001$ both). The survival plots for patients with PTDM and NoDM overlapped for approximately 96 months and thereafter those plots diverged such that, overall, the survival of PTDM was significantly lower than that of NoDM ($P = 0.04$ by log rank). A second analysis plotted survival in patients with PTDM from the time of development of diabetes, and compared with the survival in DM and NoDM calculated from the transplant day (Fig. 4B). As can be seen, the survival plots for DM and PTDM are superimposable and significantly different from the survival of NoDM ($P < 0.0001$ by log rank).

Table 3 displays the variables that, by Cox analysis, correlate significantly with patient survival in this population. It should be noted that in these analyses PTDM was analyzed as a time dependent variable. By univariate analysis the variables that correlated with reduced patient survival included: older age; male recipient; remote rather than more recent transplant year; reduced serum albumin during the first year post-transplant; DM pre-transplant; the development of PTDM; heavier recipient;

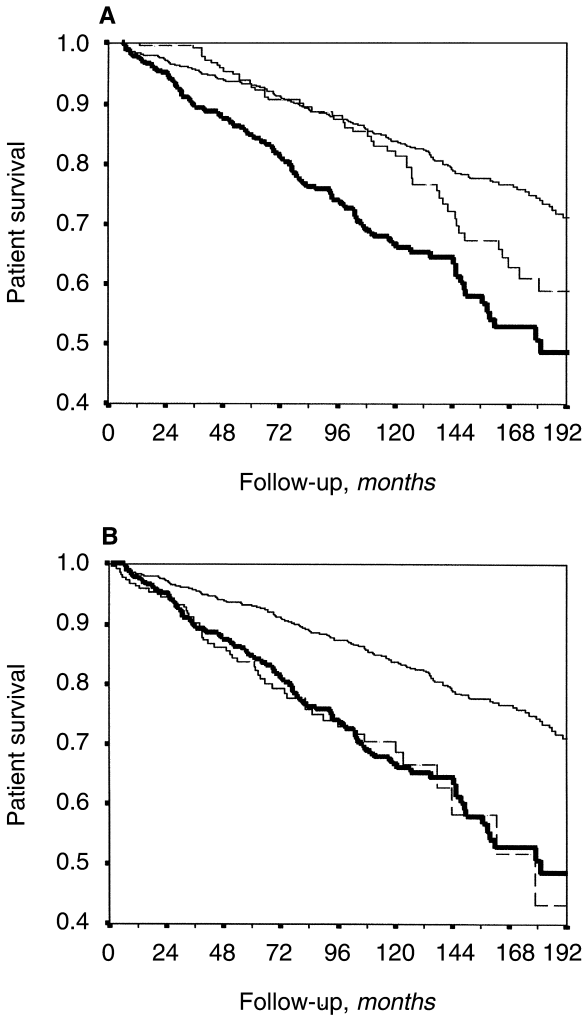

Fig. 4. Kaplan-Meier patient survival in the three study groups: NoDM (thin line), DM (thick line) and PTDM (dashed line). (*A*) Survival was calculated from the day of transplantation in all three groups of patients. (*B*) Survival for PTDM was calculated from the time of development of diabetes and for the other two groups from the day of transplantation.

elevated total serum cholesterol; elevated triglycerides; and elevated systolic BP during the follow-up period. In addition, there were significant correlations between reduced patient survival and lower diastolic BP (RR = 0.979, $P = 0.002$) and/or higher pulse pressure (RR = 1.029, $P < 0.0001$). Other variables that did not correlate significantly with patient survival included: recipient race; donor age, race or gender; number of acute rejection episodes; graft function at six months post-transplant; and histocompatibility parameters.

In a multivariate analysis, including only those patients who were not diabetic prior to the transplant (Table 3), PTDM was a significant correlate of reduced patient survival independently of other variables, including recipient age and gender, and serum albumin. The transplant year was not added to this model because we found

Table 3. Covariates of patient survival (Cox regression analysis)

Variable	Number of observations[a]	Univariable	Multivariable[c]
Age	1811	1.0 (1.03–1.05); $P < 0.0001$[b]	1.07 (1.05–1.1); $P < 0.0001$
Sex	1811	1.48 (1.16–1.89); $P < 0.0001$	NS
Transplant year	1811	0.96 (0.92–0.99); $P = 0.01$	—[g]
Serum albumin[d]	1032	0.21 (0.14–0.32); $P < 0.0001$	0.23 (0.14–0.38); $P < 0.0001$
DM pre-transplant	1811	2.2 (1.84–2.76); $P < 0.0001$	Not included
PTDM[e]	1811	1.80 (1.25–2.41); $P = 0.001$	1.88 (1.07–3.30); $P = 0.02$
Weight	1771	1.007 (1.003–1.01); $P = 0.007$	NS
Total cholesterol	1183	1.003 (1–1.005); $P = 0.04$	NS[f]
Triglycerides	1159	1.001 (1–1.001); $P = 0.01$	NS[f]
Systolic BP	1755	1.017 (1.01–1.025); $P = 0.02$	NS

[a] The number of observations in the first column refer to the univariate analysis only
[b] Values represent hazard ratio, 95% confidence interval, and P value
[c] Patients with DM before the transplant were excluded from the multivariate model
[d] Average values for serum albumin concentration between 6 and 18 months post-transplant
[e] PTDM was analyzed as a time dependent variable
[f] Cholesterol and triglycerides were analyzed separately in two different multivariate models
[g] Transplant year was not included in the multivariable model because we found collinearity between this value and PTDM

a significant co-linearity between this parameter and PTDM.

DISCUSSION

The results of this study are consistent with the interpretation that PTDM is the final manifestation of a complex metabolic profile that is thought to be the consequence of resistance to the actions of insulin [12]. This syndrome has received several names including syndrome X, insulin resistance syndrome, and dyslipidemia syndrome. Understanding PTDM as a late manifestation of the insulin resistance syndrome provides a reasonable explanation for the observation made in our current study that, in transplant recipients, the metabolic (dyslipidemia) and hemodynamic (hypertension and widened pulse pressure) abnormalities associated with PTDM precede the development of hyperglycemia.

In previous studies we discussed the variables that correlate with the development of PTDM [8]. Those variables include increasing age, increasing weight, African American race, and a transplant done in recent years. To that list we now add another independent variable, the presence of elevated serum TG levels, which correlate with the subsequent development of hyperglycemia, that is, PTDM. It is hoped that the recognition of factors that predispose to PTDM will encourage the use of post-transplant management strategies that could minimize the risk of PTDM. For example, the literature emphasizes the diabetogenic effects of chronic corticosteroid use and the more potent diabetogenic effects of FK506, compared to cyclosporine, particularly in African Americans [18, 19]. Indeed, the diabetogenic effect of steroids is one of the principal reasons for the current emphasis on the application of steroid withdrawal immunosuppressive protocols following transplantation [20]. In contrast, the potent diabetogenic effect of FK506 is rarely mentioned as a reason for avoiding the use of this drug in patients at high risk for PTDM, particularly African Americans. Perhaps this inconsistency in approach reflects an incomplete appreciation of the potentially devastating consequences of PTDM for transplant recipients.

In addition to elevated TG levels, patients with PTDM had an unfavorable cardiovascular risk profile that included obesity, elevated total serum cholesterol, elevated systolic blood pressure, and elevated pulse pressure. Of interest, these parameters did not differ significantly between patients with PTDM and patients with DM prior to the transplant, which is striking because DM is statistically the strongest predictor of patient survival after renal transplantation (for example, [6]). Perhaps this lack of difference in cardiovascular risk profile explains the observation made here that, calculated from the time of development of PTDM, the survival of PTDM and DM patients do not differ significantly. Furthermore, the hazard ratio for DM and PTDM were quite similar (2.1 and 1.88, respectively).

Among the cardiovascular risk factors considered in our current study, it was of particular interest to observe the evolution of the pulse pressure in patients with DM or PTDM. Pulse pressure was significantly higher during the first years post-transplant in DM than in PTDM, because the diastolic BP was significantly lower in patients with DM. This observation is of interest because, as shown here and also in previous studies [21, 22], low diastolic BP, particularly in association with high systolic BP, correlates with an increased cardiovascular risk. With increasing time post-transplant, the pulse pressure rose in patients with PTDM until it reached values that were not significantly different from values found in patients with DM. Pulse pressure is now recognized as a statistically strong correlate of CV risk [23, 24].

Because the measured CV risk factors were abnormal

in patients with PTDM before the development of hyperglycemia it is perhaps not surprising that PTDM correlates significantly with reduced patient survival, despite the relatively short duration of diabetes. Indeed, these observations also raise the following disturbing questions: If diabetes is only the final, late manifestation of the insulin resistance syndrome, what is the actual prevalence of this syndrome in recipients of kidney transplants? Furthermore, what is the contribution of the insulin resistance syndrome, with its associated complex metabolic and hemodynamic abnormalities, to the high cardiovascular risk of these patients?

In this study we did not analyze the morbidity associated with PTDM nor the potential impact of PTMD on graft survival. The latter effect is controversial and while some publications showed that PTDM is associated with reduced death censored kidney graft survival, others did not [reviewed in 9, 16]. Analyses of data from patients transplanted in our institution showed that PTDM is not associated with significantly reduced renal allograft survival (data not shown). However, clearly the development of diabetes, with time, will have deleterious effects on the transplanted organ. For example, anecdotally we have observed patients with PTDM who develop classic diabetic glomerulosclerosis in the allograft after more than five years post-transplant. As the survival of renal allografts and that of renal allograft recipients continues to improve [1, 2], it is inevitable that the magnitude of the negative impact of PTDM on graft and patient survival will increase. For all of the reasons proposed above, we believe that the diagnosis, prevention, pathogenesis, and treatment of insulin resistance after transplantation should be a major focus for future research.

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