



Posttransplant Diabetes Mellitus in Renal Allograft Recipients: A Prospective Multicenter Study at 2 Years

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ABSTRACT

The purpose of this study was to investigate the incidence and risk factors for the development of diabetes mellitus after kidney transplantation (PTDM). A total of 1783 nondiabetic renal allograft recipients transplanted from January 2000 to December 2002 were included. Diabetes was diagnosed following American Diabetes Association criteria. While 1276 patients were treated with tacrolimus (Tac), mycophenolate mofetil (MMF), and steroids, 507 patients received cyclosporine-ME (CsA), MMF, and steroids. PTDM incidence at 6, 12, and 24 months was 14.2%, 12.8%, and 13.3%, respectively. Cumulative incidence during the follow-up was 21.6%. Only 121 of the diabetic patients (47.6%) at 6 months remained diabetic at 24 months. Furthermore, 60 patients of 116 patients on insulin at 6 months (51.7%) remained on treatment at 24 months. The cumulative incidence of PTDM was similar in the two immunosuppressive treatments (19.7% on CsA-MMF vs 22.3% on Tac-MMF; $P = \text{NS}$). However, at 24 months, 14 of 50 diabetic patients on CsA-MMF (28%) and 74 of 161 patients on Tac-MMF (45.9%) were on insulin treatment ($P < .05$). By Cox regression analysis, age older than 60 years (RR 1.61; 95%CI 1.28–2.04; $P < .001$), body mass index (BMI) $> 30 \text{ kg/m}^2$ at transplantation (RR 1.66; 95%CI 1.27–2.16; $P < .001$), and immunosuppression with Tac (RR 1.30; 95%CI 1.02–1.66; $P = .033$) were associated with PTDM. In conclusions, the incidence of PTDM at 24 months in immunosuppressive protocols including MMF is about 22%, and it is associated with older age, increased BMI, and immunosuppression with Tac.

POSTTRANSPLANT DIABETES MELLITUS (PTDM) is a common complication of kidney transplantation, although its incidence varies depending on the criteria used for its definition. PTDM has been defined as fasting glucose above 140 mg/dL,¹ as the need for treatment either with oral hypoglycemic agents or insulin² and as the need for treatment with insulin for more than 30 days.³ Although most of the patients develop PTDM in the first 3 months after transplantation, its incidence increases with follow-up.^{2,4,5} Patient age, non-white ethnicity, higher body mass index (BMI), high doses of glucocorticoids, and immunosuppression with high doses of cyclosporine (CsA) and tacrolimus (Tac) are identified risk factors for the development of PTDM.^{1,2,4–10} Whether Tac is more diabetogenic than CsA is now under debate. The importance of PTDM is mainly its association with poor patient and graft survival^{4,6,11} and with the development of cardiovascular events.⁹ This present study aimed to deter-

mine the incidence of PTDM at 24 months after transplantation in a Mediterranean population, defining diabetes according to the American Diabetes Association (ADA) criteria¹² and to investigate the risk factors associated with this complication, placing special emphasis on the type of immunosuppression.

PATIENTS AND METHODS

From a prospective and multicenter database focused on cardiovascular risk factors and including 2600 recipients of a kidney transplant performed from January 2000 to December 2002 in 14 hospitals in Spain, a total of 1783 renal allograft transplant

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recipients were selected to be included in the study. Inclusion criteria were no previous history of diabetes mellitus and immunosuppressive treatment based on either Tac or CsA in combination with mofetil mycophenolate (MMF). Mean age of patients included in the study was 48.1 ± 12.4 years. There were 1081 males and 702 females and time on dialysis before transplantation was 39.3 ± 47.4 months. A total of 1276 patients were treated with Tac, MMF, and steroids, and 507 patients were treated with CsA, MMF, and steroids. At 6, 12, and 24 months of follow-up the following biochemical parameters were determined: serum creatinine, fasting glucose, serum cholesterol and triglycerides, and plasma levels of CsA or Tac. Diabetes was diagnosed following the ADA criteria. The results are reported as mean values \pm SD. The Student's *t* test was used to compare numerical variables and the chi-square test for categorical data. Cox regression analysis was used to determine adjusted effect of the independent variables on PTDM. Variables included in the model were age, gender, BMI, time on dialysis, hepatitis C antibody status, acute rejection, 6-methylprednisolone dosages, serum creatinine, and immunosuppression.

RESULTS

At 6 months after transplantation, 254 patients (14.2%) had developed new onset diabetes, 221 patients were diabetic at 12 months (12.8%), and 211 patients (13.3%) at 24 months. Cumulative incidence of PTDM during the follow-up was 21.6% (386 patients). A total of 116 patients were on insulin treatment, and 25 on oral antidiabetic agents (55.5%) at 6 months and 88 and 40, respectively, at 24 months. Cumulative incidence of treatment with insulin was 10.3%. However, only 121 diabetic patients (47.6%) at 6 months remained diabetic at 24 months. Furthermore, 60 patients on insulin at 6 months (51.7%) were receiving treatment at 24 months. Nevertheless, 90 of 1529 nondiabetic patients (5.9%) became diabetic at 24 months.

Compared to patients without diabetes, patients with PTDM were older than those who did not develop PTDM (53.2 ± 11.5 versus 46.8 ± 13.9 ; $P < .001$) and had higher BMI (26.4 ± 4.4 vs 24.5 ± 4.1 kg/m²; $P = .030$). There were no differences in sex distribution between PTDM patients and those without PTDM. However, when only diabetic patients at 24 months were analyzed, there was a higher percentage of females in this group than in the nondiabetic group (48.3% versus 38.8%; $P < .01$). According to immunosuppressive treatment received, cumulative incidence of PTDM in patients receiving CsA and MMF was 19.7% versus 22.3% in patients receiving Tac and MMF; this difference did not reach statistical significance. At 6 months, mean doses of Tac were 5.8 ± 3.6 mg/day in PTDM patients and 6.3 ± 3.6 mg/day in patients without PTDM ($P < .05$) and the blood Tac levels were 9.2 ± 2.9 ng/mL and 9.3 ± 3.3 ng/mL, respectively ($P = .634$). In the group under CsA, mean doses were 199 ± 83 mg/day in PTDM patients and 205 ± 83 mg/day in patients without PTDM ($P = \text{NS}$), and C₀ blood levels were 158 ± 94 ng/mL and 147 ± 83 ng/mL, respectively ($P = .808$). At 24 months, the number of patients under treatment with insulin was 74 of 161 diabetic patients (45.9%) in the Tac group and 14 of 50 diabetic patients (28%) in the CsA group ($P < .05$). By multivariate

Cox regression analysis, only age at transplant older than 60 years (RR 1.61; 95%CI 1.28–2.04; $P < .001$), BMI at transplant higher than 30 kg/m² (RR 1.66; 95%CI 1.27–2.16; $P < .001$) and immunosuppression with Tac (RR 1.30; 95%CI 1.02–1.66; $P = .033$) were associated with PTDM.

DISCUSSION

Our results indicate that the incidence of PTDM using the ADA definition criteria was quite similar to that reported from the United States Renal Data System⁴ or from single center studies.^{9,10} However, lower incidences have been observed in other single-center studies.⁸ One important point we have observed is that about 50% of diabetics at 6 months were not diabetic at 24 months. These findings are different from those reported by Cosio et al,⁹ who showed that 89% of patients with PTDM at 1 year had hyperglycemia at 1 week and from that of Gourishankar et al,⁸ who observed resolution of PTDM defined by discontinuation of oral antidiabetic agents or insulin in 10.5% of cases. We do not know the causes of these differences. In the analysis of risk factors for PTDM, older age, obesity (defined by BMI higher than 30 kg/m²) and immunosuppression with Tac were the only risk factors identified in our study. Age at the time of transplantation has been considered one of the strongest predictors of risk for PTDM and the most frequently found risk factor.^{2,4,5,7–11} Obesity^{2,4,8,9} as well as increase in body weight after transplantation⁷ are strong risk factors of PTDM in most series. The calcineurin inhibitors CsA and Tac cause PTDM by multiple mechanisms. Whether Tac is more diabetogenic than CsA is now under debate. Two metaanalysis^{13,14} of randomized trials comparing Tac and CsA in renal transplant recipients concluded that Tac was more diabetogenic than CsA in this patient population. These results were confirmed on registry data^{4,5} and single-center studies.^{15,16} However, in a randomized trial³ comparing Tac and CsA in combination with MMF, the incidence of diabetes was similar with both immunosuppressive drugs. In this trial, PTDM was defined as the need for insulin treatment for more than 30 days. In the present prospective study, we did not find any differences in the incidence of PTDM between Tac- or CsA-treated recipients in the univariate analysis. However, when adjusted for other variables, immunosuppression with Tac was a weak but significant risk factor for the development of PTDM. Our results did not agree with those in which PTDM was related to high blood levels of both CsA⁷ and Tac.¹⁵ Diabetic patients were taking lower doses of both Tac and CsA than nondiabetics in our study. This finding could be due to an intentional decrease in the dose of calcineurin inhibitors when diabetes appeared or to modified metabolism of Tac in diabetics because diabetic patients under Tac were receiving lower doses than nondiabetics, but the blood levels of Tac were similar in both groups. Diabetic patients taking Tac were more frequently treated with insulin than diabetics taking CsA, which could be attributed to a more severe diabetes in the former group.

As in another study performed in Spain,¹⁷ we did not find any association between PTDM and hepatitis C antibody status as has been reported in other studies,^{4,8,16} although 7% of our patients had antibodies against hepatitis C virus.

In conclusion, the prevalence of PTDM in our series at 24 months was 13.3%, and the cumulative incidence was around 22%. Older age, obesity, and immunosuppression with Tac were the only risk factors identified for the development of PTDM.

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