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ORIGINAL ARTICLE

Post-transplant diabetes mellitus: a case-control analysis of the risk factors

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Summary

Aim of the present study was to assess, in a pair-matched analysis design, risk factors for post-transplant diabetes mellitus (PTDM) in renal transplant recipients (KTx). The incidence of PTDM was evaluated in 538 consecutive KTx in relation to their baseline immunosuppression. PTDM was defined according to the 2003 American Diabetes Association and World Health Organization experts committee definition. As risk factors for PTDM development were considered: age, family history of diabetes, body mass index (BMI), baseline immunosuppression, doses and blood levels of the immunosuppressive agents used. Baseline immunosuppression consisted of CSA, TAC and SRL + CNI. Thirty-two pair-matched controls were identified among the 538 KTx and included in the risk analysis. Significant risk factors for the development of PTDM were identified in the family history of diabetes ($P < 0.02$) and BMI ($P < 0.05$). Higher BMI and positive family history for diabetes mellitus were significant risk factors for the development of PTDM, regardless of the immunosuppressive agent used.

Introduction

Post-transplant diabetes mellitus (PTDM) is a major adverse effect of current immunosuppression after kidney transplantation. The incidence of PTDM reported in the literature is wide, between 2% and 53% [1–4] and varies according to the definition of diabetes mellitus adopted, the type of immunosuppressive medications used and other factors. Although there are currently no clearly established risk factors for PTDM, a number of characteristics have been identified that appear to predispose patients to the development of this condition [5] such as age, ethnicity, obesity, glucose intolerance, family history of diabetes and hepatitis C virus pretransplant infection.

Aim of the present study was to assess potential risk factors for PTDM in a pair-matched cohort of renal transplant recipients (KTx) treated with different immunosuppressive regimens.

Materials and methods

The incidence of PTDM was retrospectively evaluated in 538 consecutive KTx performed at the Catholic University of Rome, Italy from January 1981 to December 2002. Baseline immunosuppression was azathioprine (AZA) in 62 patients (11.5%), cyclosporine (CsA) in 328 patients (60.9%), tacrolimus (TAC) in 92 patients (17.1%) and sirolimus + calcineurine inhibitors (SRL + CIN) in 48 patients (8.9%). All patients received steroids for induction and prednisone dosage was tapered in order to reach a standard maintenance dose of 5 mg/day by the end of the third postoperative month. Over 90% of patients were on continuous steroid maintenance therapy, <10% of patients were included in steroid-free experimental protocols, PTDM was defined according to the American Diabetes Association (ADA) and World Health Organization (WHO) experts committee definition [6] as fasting blood glucose levels

of 126 mg/dl or greater was confirmed by repeated testing on a different day.

Thirty-six KTx developing PTDM were identified within the entire cohort and four of these were considered noneligible for the present analysis, because of incomplete data or lack of appropriate matched controls. The remaining 32 were included in the study along with 32 pair-matched controls. Pair-matched controls were selected by age at transplant (±2 years) and date of transplantation (±6 months). Patients' characteristics within the two groups are presented in Table 1. There were no discordant pairs. Patients with diabetic pretransplant were excluded from the present analysis. As risk factors for PTDM development were considered: recipient age at the time of transplantation, family history of diabetes, body mass index (BMI), baseline immunosuppressive agents, their doses and blood levels at predefined time points (6 months, 1, 3, 5 years post-transplant). Data were entered into an Excel (Microsoft) database and queried as appropriate for median or mean ± SD. Paired Student's *t*-test and chi-square test were used to compare the differences between the measurements, multiple regression analysis was also performed using Smith's Statistical Package (version 2.5 by Gary Smith, Pomona College, Claremont, CA, USA) to assess the independent contribution of the risk factors.

Results

There were no differences between the two groups in terms of age, sex, baseline immunosuppressive agents, their doses and blood levels at 6 months, 1, 3 and 5 years post-transplantation (Tables 1 and 2). Mean follow-up of KTx in the study group was 50.1 ± 6.5 months (range 17–60).

PTDM

Thirty-one patients required insulin treatment (three in AZA, 16 in CsA, six in TAC and six in SRL + CIN) and five patients required oral antidiabetic medications (zero patients in AZA, three in CsA, one in TAC, one in SRL + CIN) to normalize their blood glucose. The incidence of family history of diabetes was higher in the PTDM group compared to controls: eight (25%) vs. two (6.2%) patients, ($P < 0.03$); mean BMI was also higher in this group (25 ± 3.9 vs. 22.9 ± 6.1, $P = 0.05$). PTDM occurred 25.3 ± 38 months after transplantation, the time of onset was significantly shorter ($P = 0.003$) in the TAC group (2.1 ± 1.7 months post-Tx, range 0–4.3 months) compared with CsA (27.8 ± 24 months post-Tx, range 0–52.9 months). In six of 32 patients (18.7%) Table 3 PTDM disappeared 11 ± 21 months after onset (range 8.1–32.4 months), spontaneously in four patients and after steroid withdrawal in two patients. Disappearance of PTDM occurred at an earlier time in 1 patient on TAC (8.1 months) versus five patients on CsA (22.4 ± 8.5 months). Multivariate analysis of the potential risk factors for the development of PTDM was conducted by matching the dependent variable PTDM with a series of recipient demographic and immunosuppressive factors: age, BMI, family history of diabetes, serum creatinine, type of immunosuppressant (TAC, CsA or SRL), immunosuppressive drug doses and blood levels. Again two significant risk factors for the development of PTDM were identified: family history of diabetes and BMI ($P < 0.02$ and $P < 0.05$, respectively) (Table 4).

Table 1. Patient demographics and immunosuppressive agents used.

Parameters	PTDM	Controls	*P*
No. of patients	32	32	
Age	46 ± 12	46 ± 10	NS
Sex	20M/12F	19M/13F	NS
Family history	8	2	0.03
BMI	25 ± 3.9	22.2 ± 6.1	0.05*
Time post-Tx	49.7 ± 16.5	50.3 ± 14.7	NS
TAC	11	11	NS
CsA	21	21	NS
SRL + CIN	8	7	NS
Steroids	31	29	NS
MMF	4	7	NS
AZA	2	2	NS

*Statistically significant.

PTDM, post-transplant diabetes mellitus; BMI, body mass index; TAC, tacrolimus; CsA, cyclosporine; SRL, sirolimus; CIN, calcineurine inhibitors; AZA, azathioprine; NS, not significant; MMF, mycophenolate mofetil.

Table 2. Blood levels of immunosuppressive agents.

	Patients (*n*)	PTDM	Patients (*n*)	Controls	*P*
CsA C0 blood levels					
Discharge	21	373 ± 242	21	461 ± 331	0.40
3 m	21	222 ± 148	21	252 ± 116	0.39
6 m	21	253 ± 162	20	254 ± 134	0.96
1 year	21	276 ± 162	20	202 ± 167	0.10
3 year	19	234 ± 168	19	193 ± 89	0.13
5 year	17	139 ± 81	17	151 ± 71	0.26
TAC C0 blood levels					
Discharge	11	13.7 ± 7.3	11	11.3 ± 8	0.49
3 m	11	11.6 ± 4.9	10	10.8 ± 4.6	0.86
6 m	10	9.3 ± 5.1	10	9.3 ± 6.1	0.62
1 year	9	7.8 ± 4.6	9	7.1 ± 4.8	0.90
3 year	7	9.7 ± 3.1	9	7.2 ± 4.9	0.17
5 year		NA		NA	

PTDM, post-transplant diabetes mellitus; CsA, cyclosporine; TAC, tacrolimus; NA, not available.

Table 3. Characteristics of patients with PTDM disappearance.

	PTDM disappeared	PTDM nondisappeared	No PTDM matched controls
No. of patients	6	26	32
Time since Tx (months)	51.3 ± 14.7	49.6 ± 16.4	50.3 ± 14.7
Time of PTDM onset	11 ± 21	10 ± 15.1	NA
Time of PTDM disappearance (months)	18.2 ± 12.2	NA	NA
On maintenance steroid therapy	4/6 (66%)	26/26 (100%)	30/32 (94%)
Immunosuppression			
CsA	4	14	17
TAC	1	5	8
SRL + CIN	1	7	7
Family history of diabetes	40%	33%	6%
BMI	25.8 ± 1.9	25 ± 4	22.2 ± 6.1

PTDM, post-transplant diabetes mellitus; BMI, body mass index; TAC, tacrolimus; CsA, cyclosporine; SRL, sirolimus; CIN, calcineurine inhibitors; NA, not available.

Table 4. Multiple regression analysis of PTDM risk factors.

Parameters	Coefficient	Standard error	*t*-Value	*P*
Age	0.0060	0.0069	0.8650	0.1958
Sex	−0.0507	0.1381	0.3668	0.3577
Family history	0.03967	0.2022	1.9621	0.0279*
BMI	0.0396	0.8434	1.9434	0.0104*
Creatinine	−0.1296	0.0868	1.4923	0.0712
TAC	0.0101	0.1446	0.0695	0.4724
CsA	−1.1424	0.8182	1.3963	0.0844
SRL + CIN	−0.0054	0.1513	0.0357	0.4859
Steroids	0.2128	0.3011	0.7066	0.2417

*Statistically significant.
PTDM, post-transplant diabetes mellitus; BMI, body mass index; TAC, tacrolimus; CsA, cyclosporine; SRL, sirolimus; CIN, calcineurine inhibitors.

Renal function, graft and patient survival

Renal function, graft and patient survival at 6 months, 1, 3, 5 years from transplantation were not different in the two groups (Figs 1 and 2). Mean serum creatinine levels decreased from 1.9 ± 0.6 mg/dl at discharge to 1.5 ± 0.4 mg/dl at the latest follow-up in the PTDM group and from 1.7 ± 0.9 to 1.5 ± 0.5 at the latest follow-up in controls. Five years of patient survival was slightly lower in PTDM that in controls (90% vs. 94.8% $P = 0.58$), but not statistically different. Five years graft survival in PTDM and in controls was 85% and 84.3% ($P = 0.94$) respectively (Fig. 2).

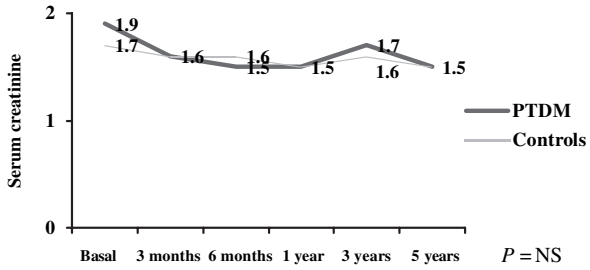

Figure 1 Graft function.

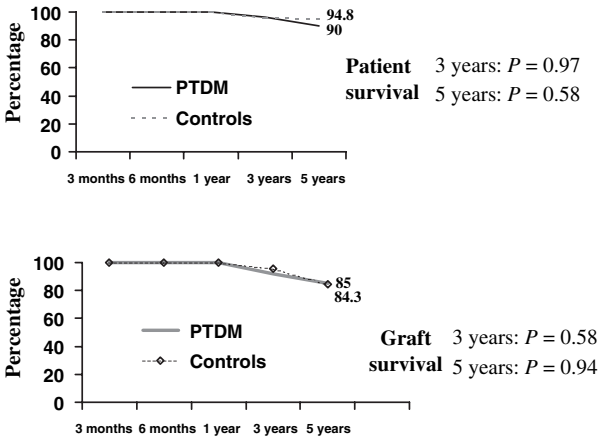

Figure 2 Patient and graft survival.

Discussion

This study evaluated risk factors for the development of PTDM after renal transplantation. The incidence of PTDM reported in the literature ranges between 2% and 53% [10] depending on the definition of diabetes adopted. We adopted the American Diabetes Association (ADA) and World Health Organization (WHO) experts committee definition of diabetes [6], to decide on PTDM. The present analysis revealed that higher BMI and positive family history for diabetes mellitus are the significant risk factors for the development of PTDM, regardless of the immunosuppressive agent used. It has been previously demonstrated that the type of immunosuppression can explain up to 74% of the variability in diabetes incidence [7], but in our study the immunosuppressive agent did not emerge as a significant risk factor for PTDM development. A possible explanation for this finding is the low doses of steroid administered in our protocols and the use of meticulous therapeutic blood level monitoring of the immunosuppressive agents, avoiding prolonged high CNI exposure, a well-known hazard. In particular, levels of immunosuppression were not significantly different between patients with or without PTDM. However, a

difference became clear between CsA and TAC on the timing of PTDM onset: in TAC patients PTDM occurred soon after Tx, while in CsA patients PTDM appeared to be a late complication. BMI is a well-recognized risk factor for wound and cardiovascular complications after renal transplantation, our data indicate that BMI is also a potent risk factor for PTDM development. Therefore, patients with higher BMI should be convinced to reduce their weight before transplantation. PTDM has been associated with reduced graft function, reduced patient survival and increased graft loss [8,9]. Previous study has also indicated that the consequences of post-transplant diabetes mellitus are similar to those of pretransplant diabetes mellitus [10]. We were not able to show a significant detrimental effect of PTDM on graft and patient survival. A possible explanation could be the early diagnosis and the prompt treatment of PTDM adopted, which may have avoided severe damages induced by prolonged unrecognized hyperglycaemia. Therefore, early detection, prevention and treatment of diabetes mellitus are essential to reduce the frequency of severe complications in renal transplant recipients.

In conclusion, we suggest that high BMI and family history of diabetes are the most important factors in the development of PTDM, regardless of the baseline immunosuppressive agents. In these high risk patients the immunosuppressive regimen should be carefully monitored to avoid toxic combinations, favouring the development of PTDM, and every effort should be encouraged towards an early diagnosis of PTDM.

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