Port J Nephrol Hypert 2008; 22(4): 319-324

Risk factors for posttransplant diabetes mellitus

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Received for publication: 08/01/2008
Accepted in revised form: 18/08/2008

ABSTRACT

Background: Posttransplant diabetes mellitus is a serious complication of renal transplantation and one associated with increased morbidity and mortality. The aim of this study was to identify the risk factors for posttransplant diabetes mellitus development.

Methods: We retrospectively evaluated 376 renal transplant recipients at a single centre. Posttransplant diabetes mellitus was diagnosed in line with the American Diabetic Association criteria. Data was collected on the recipient's age, gender and body mass index at the time of transplantation and one year after, aetiology of kidney disease, HLA mismatches, cold ischaemia time, hepatitis C infection, acute rejection episodes, use of steroid pulses and the type of immunosuppression. Patients were divided into two groups: Group 1 (n=65), patients with posttransplant diabetes mellitus and Group o (n=311), patients without the disease.

Results: The prevalence of posttransplant diabetes mellitus was 21% and the mean time from transplantation to the diagnosis of this disease was 15±27 months. Univariate analysis showed that patients who developed this disease were older (52±8.8 *vs.* 42.2±12.9 years; p<0.001), had greater baseline body mass index (26.4±3.5 *vs.* 23.7±3.7; p<0.001) and more autosomal-dominant polycystic kidney disease (21.5% *vs.* 10.6%; p=0.017). The number of acute rejection episodes, steroid pulses, use of tacrolimus and hepatitis C infection was similar between groups. Multivariate analyses showed that age and baseline body mass index were independent risk factors for developing this disease.

Conclusions: Age and baseline body mass index were risk factors for the development of posttransplant diabetes mellitus. The identification of a risk profile for the development of this disease should be considered in the pretransplant period, when attempts to reduce some modifiable factors must be made. Further studies are needed to clarify the most important predictive factors and the best strategies to prevent and minimise the long term consequences of this disease.

Key-Words:
Diabetes mellitus posttransplant; renal transplantation; risk factors.

INTRODUCTION

Posttransplant diabetes mellitus (PTDM) is a serious metabolic complication of renal transplantation. The reported impact of this disease on patient and graft survival[1,2] has raised great concern over the prevention of this condition and the long-term management of renal transplant recipients who develop the disease.

The real incidence of PTDM in the transplant population is not known. Published studies in this field report an incidence that ranges from 2 to 53%[3]. This variability is a consequence of using multiple criteria for PTDM diagnosis. Nevertheless, the number of cases has increased significantly[4] since 1995.

The importance of immunosuppressive agents in the physiopathology of PTDM has long been recognised.

Corticosteroids and calcineurin inhibitors have been shown to increase insulin resistance and decrease insulin secretion due to ß-cell toxicity[5,6].

Although the role of immunosuppression is recognised, some clinical features of PTDM have led to the hypothesis that other mechanisms may be involved. Like type 2 diabetes mellitus, PTDM has an insidious course. Patients may remain asymptomatic for long periods and the disease can, in some cases, be reversed with control of some associated conditions[7]. This clinical similarity suggests that the same factors may predispose towards both conditions.

The aim of this study was to identify possible risk factors for the development of PTDM. We retrospectively evaluated our kidney transplant population, calculated the prevalence of this disease and studied the importance of some clinical features. We then compared a group of patients with PTDM with a control group of renal transplant recipients without this disease.

PATIENTS AND METHODS

In this study we evaluated 376 patients transplanted in a single centre between 1990 and 2006.

PTDM was defined in line with the diagnostic criteria of the American Diabetes Association[8]: symptoms of diabetes plus casual glucose concentration ≥200mg/dl or fasting plasma (FPG) glucose level ≥126mg/dl (fasting is defined as no caloric intake for at least 8 hours) or 2h post load glucose ≥200 mg/dl during an oral glucose tolerance test. All patients in the study had at least one FGP or casual glucose determination in a three month interval and all abnormal values were confirmed by another laboratory evaluation prior to diagnosis. Patients with diabetes mellitus prior to renal transplant and those meeting the criteria in the first month posttransplant were excluded.

Clinical characteristics collected at the time of transplantation were the recipient's age, gender, height, weight, body mass index (weight/height^2), cause of kidney disease, HLA mismatches, cold ischaemia time and hepatitis C infection (HCV). During the posttransplant period the presence of acute rejection, use of steroid pulses and the type of immunosuppression were recorded. Another evaluation of body mass index (BMI) based on patient's height and weight after one year of transplantation was performed and the Δ BMI (BMI at 1 year- baseline BMI) calculated.

The study population was divided into two groups depending on the presence of PTDM: Group 1 (n=65), patients with new-onset diabetes and Group 0 (n=311), patients without the disease.

The data are expressed as means±SD. Means were compared between the two groups using the Student *t* test or by a non-parametric test if the data were not normally distributed. Categorical variables were compared using the chi-square test. Risk factors for PTDM were evaluated by multiple logistic regression analyses.

RESULTS

Description of data for univariate analyses of the various factors evaluated in the two groups are shown in Table I. The mean follow up period was 62.8±48 (210-0.5) months.

The prevalence of PTDM in the study population was 21%. The incidence of this disease along time is shown in Fig. 1. The mean time from transplantation to diabetes diagnosis was 15±27 months, but

Table I

Patient characteristics evaluated in the two groups

	Group 1 (PTDM)	Group 0	p
n	65	311	
Age mean±sd (years)	52±8.8	42.2 ±12.9	p<0.001
Gender % males	67	65	p=ns
Baseline BMI- mean±sd	26.4±3.5	23.7 ±3.7	p<0.001
HCV %	13.8	14.7	p=ns
ADPKD %	21.5	10.6	p=0.017
HLA mismatches -mean±sd	3.1±1	3.2±0.9	p=ns
Cold ischaemia time-mean±sd	20.5±4.6	19.7±4.4	p=ns
Steroid pulses %	46	40	p=ns
Tacrolimus %	7	8	p=ns
Acute rejections %	46	40	p=ns

BMI – Body mass index; **HCV** – hepatitis C virus; **ADPKD** – autosomal-dominant polycystic kidney disease.

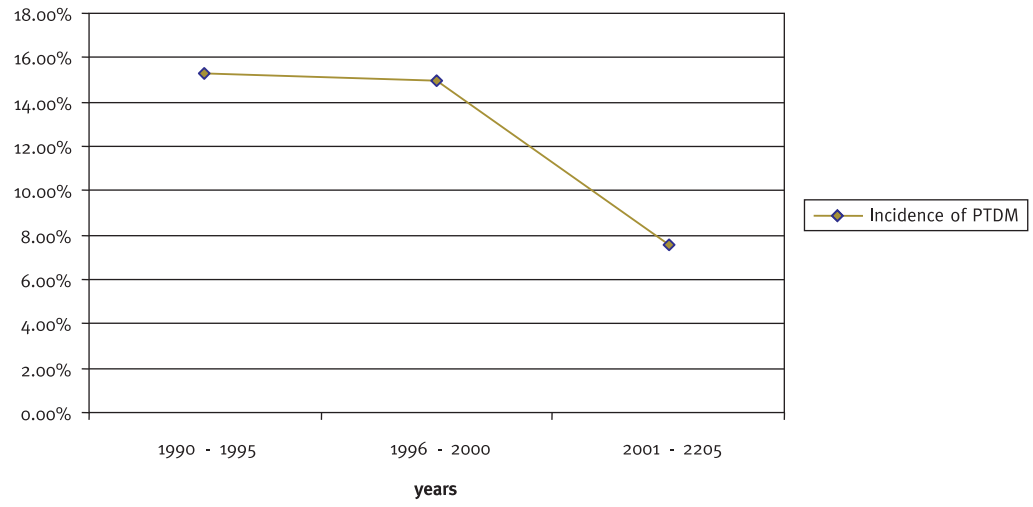

Figure 1

Incidence of PTDM in the study population along time.

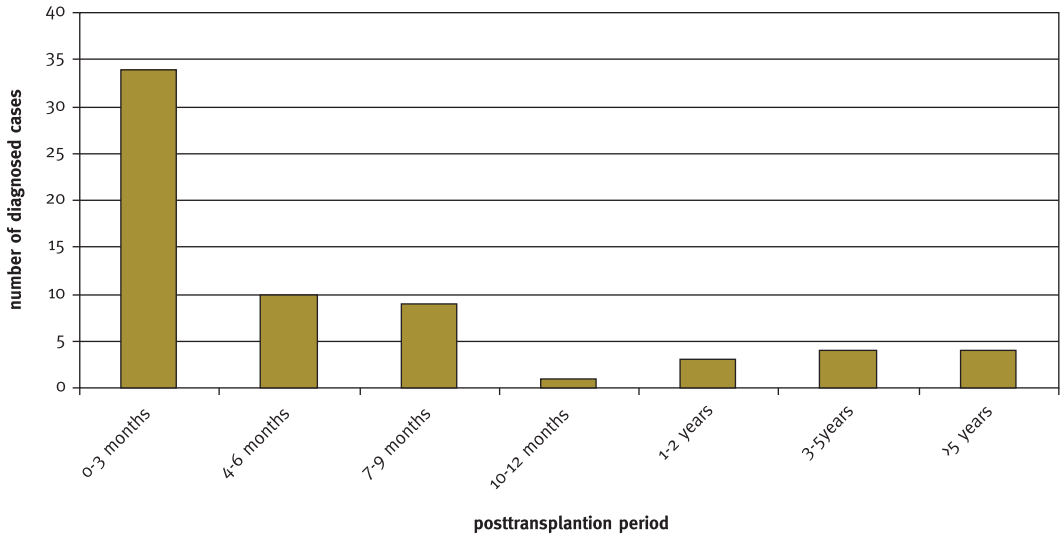

Figure 2

PTDM diagnosis along the posttransplantation period.

67.6% of the patients developed the disease within the first 6 months of transplantation (Fig. 2).

PTDM group patients were significantly older at time of transplantation (52±8.8 *vs.* 42.2±12.9 years; p<0.001). Baseline body mass index (Fig. 3) was higher in the diabetic patients (26.4±3.5 *vs.* 23.7±3.7; p<0.001). In the majority of patients, while body weight increased in the first 12 months posttransplantation, the mean Δ BMI was similar between groups (Fig. 4), indicating that the mean increase of body weight after that period did not differ significantly between patients who developed diabetes and those who did not.

Regarding the cause of kidney disease, there was a higher percentage of patients with autosomal

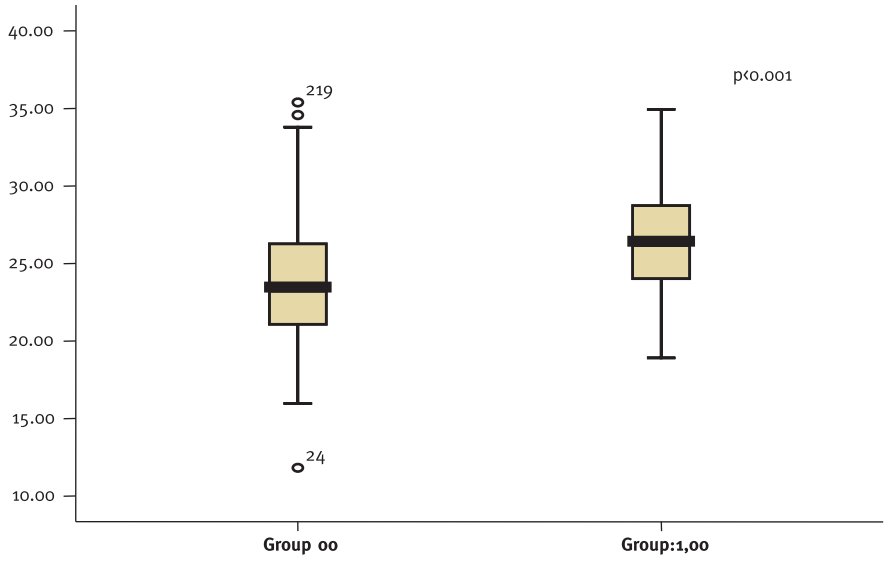

Figure 3

Baseline body mass index compared between groups.

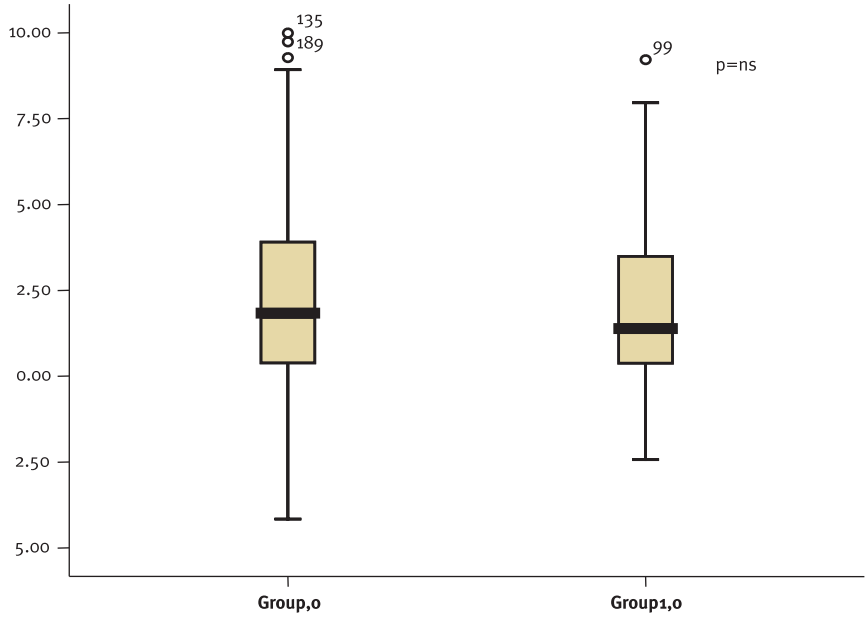

Figure 4

Δ Body mass index (BMI at 1 year- baseline BMI) in the two groups.

dominant polycystic kidney disease (ADPKD) in the group with PTDM (21.5% *vs.* 10.6%; p=0.017).

The number of acute rejection episodes, steroid pulses and HCV infection was similar in both groups.

All patients in the study population had an immunosuppression scheme that included calcineurin inhibitors (CNIs) and prednisolone, with 47% also treated with azathioprine and 53% with mycophenolate mofetil. Induction therapy was used in 97/376

patients (75% with basiliximab, 25% with ATG) There was no significant difference between groups in the number of patients treated with tacrolimus.

In multivariate analyses only age (OR=1.2, 95% CI=1.15-1.29; p=0.02) and baseline BMI (OR=1.5, 95% CI=1.3-1.71; p=0.01) were independent risk factors for the development of PTDM.

DISCUSSION

Significant improvements in immunosuppression therapy in the past two decades have diminished the rate of early graft failure and increased its half-life[9]. Consequently there has been greater concern over the long-term complications of renal transplantation. Death with functioning allograft is a major cause of late graft loss and this mortality is related to cardiovascular disease in many cases[10,11]. Diabetes mellitus appears to be one of the most important cardiovascular risk factors identified in the transplant population[12].

In the past, the importance of PTDM was underestimated because it was generally thought that this condition was not associated with the serious complications observed in other types of diabetes. In recent years it has been recognised that posttransplant diabetes is associated with micro and macrovascular complications[13] and with reduced patient and graft survival[1,2].

As shown here and in other previous studies, patients who developed new-onset diabetes were older and had a higher BMI at time of transplantation[4,14]. Other variables mentioned in the literature but not investigated in our work, such as dyslipidemia, hypertension and widened pulse pressure, have been associated with PTDM and precede the presence of hyperglycaemia. These findings are consistent with the likely presence of an insulin resistance syndrome and PTDM may be its final manifestation[1,14]. It is therefore probable that these risk factors, in many cases already present in the pretransplant period, increase the patient's susceptibility to the diabetic effects of immunosuppressive drugs.

The significance of the pretransplant period is well documented in our study and others[4] since the difference of weight at time of transplantation is more important than the amount of weight gain in the first year of transplantation.

All of these related co-morbidities confer an unfavourable cardiovascular risk profile[10,12] which may be responsible for the impact on patient survival seen with this type of diabetes, despite the short course of this disease.

Some authors have correlated insulin resistance syndrome with the development of chronic renal transplant dysfunction[15]. This observation might also justify the reduction in death censored graft survival seen in patients with PTDM[8].

In our study, autosomal-dominant polycystic kidney disease was the cause of kidney disease in a higher percentage of cases in the diabetic group. A similar observation was made by the authors of a recently published study which showed that patients with APKD were at a threefold risk of developing diabetes within the first year of transplantation[16]. The mechanism responsible for this association is not entirely understood. Nevertheless the association between the two diseases is controversial since a matched-pair design multicentre study published in 2008 did not consider APKD a risk factor for the development of PTDM[21].

Knowledge of the above mentioned predictive factors can be used to identify patients at high risk of developing PTDM. This screening must begin in the pretransplant period, when efforts must be made to encourage exercise and avoid obesity. Equally so, this diabetic profile must be taken into consideration in the posttransplant period when choosing the immunosuppressive therapy[17]. The diabetogenicity of current immunosuppressors differs significantly. Corticosteroids and calcineurin inhibitors have been associated with a greater risk of PTDM development[18]. Even in the same pharmacological group some drugs have been shown to be more diabetogenic than others, for instance, tacrolimus when compared with ciclosporin[19]. In our study this drug was not associated with a higher incidence of PTDM, but this observation may be the result of the small number of patients treated with this immunosuppressor. Recently a significant improvement of glycaemia and Hb A1c blood levels has been seen in patients with PTDM treated with tacrolimus when switched to ciclosporin[20].

It is also advisable to reduce the corticosteroid dose as soon possible in patients at risk of developing diabetes, since it has been shown to improve patient glucose tolerance[17].

In conclusion PTDM is an increasing complication of renal transplantation and further studies are needed to clarify the best strategies to prevent and minimise the long term consequences of this disease.

Conflict of interest statement. None declared.

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