Posttransplant Diabetes Mellitus in Kidney Allograft Recipients at Shaheed Hasheminejad Hospital

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Original Paper

Introduction. Our aim was to evaluate the frequency and risk factors of posttransplant diabetes mellitus (PTDM) at our kidney transplant center, and to compare graft and patient outcomes between the kidney recipients with and without PTDM.

Materials and Methods. We studied 203 kidney transplant recipients with a negative history of diabetes mellitus before transplantation. We examined them for PTDM and made diagnosis on the basis of the American Diabetes Association criteria. Measurements of plasma glucose were carried out from 3 months to 24 months after transplantation. All data including recipient and donor demographics, cause of end-stage renal disease, cytomegalovirus and hepatitis C virus antibody tests, and patient and graft outcomes were assessed in relation to PTDM.

Results. High fasting plasma glucose was seen in 24 (11.8%), 19 (9.4%), 16 (7.9%), and 13 (6.4%) patients at 3, 6, 12, and 24 posttransplant months, respectively. Moreover, impaired glucose tolerance was seen in 17 (8.4%), 16 (7.9%), 17 (8.4%), and 19 (9.4%) patients at the corresponding times, respectively. Accordingly, 39 patients (19.2%) were diagnosed to have PTDM. The mean age of the kidney recipients with PTDM was 46.5 ± 12.3 years as compared to 38.6 ± 13.4 years in nondiabetic kidney recipients (P = .02). The 5-year patient and graft survival rates were not significantly different between the kidney recipients with and without PTDM.

Conclusions. This study showed that PTDM is a common metabolic disorder in our kidney transplant patients. We recommend a less diabetogenic immunosuppressive protocol, especially for our older recipients.

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INTRODUCTION

During the past decade, patient and graft survival rates after transplantation have been improved and attention has been placed on nonimmunologic factors that contribute to morbidity and mortality in kidney transplant patients. Data have shown that posttransplant diabetes mellitus (PTDM) increases the rate of cardiovascular disease and infection, and that it is a major cause of morbidity and mortality.[1,2] Risk factors for PTDM such as obesity, family history of diabetes mellitus (DM), and ethnicity are similar to those for general population, but there are some risk factors unique to transplant patients. We planned a retrospective study to evaluate the

frequency and risk factors of PTDM as well as graft and patient survival rates among patients who develop this complication in comparison with nondiabetic kidney transplant recipients.

MATERIALS AND METHODS

The study group consisted of 203 kidney transplant recipients with a negative history of DM before transplantation. They received their kidney allografts from January 2001 to March 2005 at Shaheed Hasheminejad Hospital in Tehran, Iran. On the basis of the American Diabetes Association criteria,[3] PTDM was diagnosed in patients with a fasting plasma glucose (FPG) greater than 126 mg/dL or impaired glucose tolerance (IGT) while having a FPG between 100 mg/dL and 125 mg/dL. Since some patients received intravenous dextrose-containing solutions during the first posttransplant month, DM was diagnosed on the basis of the measurements of plasma glucose carried out from 3 months to 24 months after transplantation. All data including recipient and donor demographics, cause of end-stage renal disease, cytomegalovirus and hepatitis C virus (HCV) antibody tests, and patient and graft outcomes were retrieved from hospital and follow-up records.

Immunosuppressive protocol was triple therapy including cyclosporine, mycophenolate mefotil, and prednisolone. They received pulse therapy by methylprednisolone, 1000 mg, for 3 days from the day before transplantation. All patients received prednisolone, 1 mg/kg, after methylprednisolone pulse. The prednisolone dose was tapered to 5 mg/d, 6 months after transplantation in all recipients. The HCV antibody was negative and cytomegalovirus immunoglobulin G test was positive in all patients. The chi-square and the *t* test were used for univariate analyses of data, the Kaplan-Meier method and log-rank test were applied for calculation and comparisons of patient and graft survival rates. A *P* value less than .05 was considered significant.

RESULTS

There were 127 men (62.6%) and 76 women (37.4%) with a mean age of 39.4 ± 13.6 years. A high level of FPG was found in 24 (11.8%), 19 (9.4%), 16 (7.9%), and 13 (6.4%) patients at 3, 6, 12, and 24 posttransplant months, respectively. Moreover, IGT was seen in 17 (8.4%), 16 (7.9%), 17 (8.4%), and 19 (9.4%) patients at the corresponding times, respectively. The mean age of the kidney recipients with PTDM was 46.5 ± 12.3 years as compared to 38.6 ± 13.4 years in nondiabetic kidney recipients (P = .02). Overall, 39 patients (19.2%) were diagnosed to have PTDM. The recipient's weight and gender, the donor's age and gender, source of the kidney allograft, and cause of end-stage renal disease were not the risk factors of PTDM in our study (Table). The 5-year graft survival rate in the

Patient Characteristics in New-Onset Diabetic and Nondiabetic Kidney Transplant Recipients

Parameter	Diabetic Group (n = 39)	Nondiabetic Group (n = 164)	*P*
Recipient age, y	46.5 ± 12.3	38.6 ± 13.4	.02
Recipient sex			
Male	29 (74.4)	98 (59.8)	
Female	10 (25.6)	66 (40.2)	.09
Recipient weight, kg	70.7 ± 14.6	64.6 ±13.2	.15
Donor age, y	28.1 ± 5.2	28.2 ± 6.6	.92
Donor weight, kg	69.8 ± 11.6	67.7 ± 10.9	.97
Donor sex			
Male	29 (74.4)	140 (85.4)	
Female	10 (25.6)	24 (14.6)	.45
APCKD†	4 (10.3)	16 (9.7)	.74
Donor source			
Living related	3 (7.7)	10 (6.1)	
Living unrelated	35 (89.7)	152 (92.7)	
Cadaveric	1 (2.6)	2 (1.2)	.72
Second transplant	0	10 (6.1)	.15
Infection episodes	5 (12.8)	27 (16.5)	.11

*Values of quantitative variables are shown as mean standard deviation. Values in parentheses are percents.
†APCKD indicates autosomal dominant polycystic kidney disease as the primary cause of end-stage renal disease.

patients with PTDM was 95.5% which was not significantly lower than that in kidney recipients without PTDM (97.8%; P = .42), and the 5-year patient survival rates were 95.5 % and 97.9% in the two groups, respectively (P = .41).

DISCUSSION

Diabetes mellitus is a prevalent metabolic disease after transplantation. Higher ages, body mass index higher than 30 kg/m^2, African-American and Hispanic ethnicities, and family history of DM are risk factors of PTDM after transplant, as they are in healthy individuls.[4] However, there are some specific factors that increase the PTDM risk after kidney transplantation. Kasiske and colleagues[5] showed that DM occurred in approximately 9%, 16%, and 24% at 3, 12, and 36 months posttransplantation, respectively, in 11 659 kidney recipients. In their study, risk factors of PTDM were age, African-American race, Hispanic ethnicity, male donor, increasing human leukocyte antigen (HLA) mismatches, HCV infection, body mass index greater than 30 kg/m^2, and tacrolimus as the initial maintenance immunosuppressive drug. The use of mycophenolate mofetil, azathioprine, younger recipient age, glomerulonephritis as a cause of kidney failure, and higher education were the factors that reduced the risk of PTDM.[5] Increased HLA mismatches, donor-recipient mismatch, and specifically, the B27 phenotype were associated with an increased risk of PTDM, although there is inconsistency regarding the risk with specific HLA types.[5] Male and deceased donors of allografts have also been associated with PTDM in some studies.[1] In a systematic review by Fabrizi and coworkers,[6] a significant link between anti-HCV seropositive status and DM after kidney transplantation was shown (odds ratio, 3.97). Cytomegalovirus infection has also been reported to increase the risk of PTDM. In one study, an asymptomatic cytomegalovirus infection was associated with a lower median insulin release and a four-fold increased risk of PTDM.[7] Polycystic kidney disease may confer an increased risk of PTDM, although this has not consistently been observed.[8]

Immunosuppressive drugs have an important role in the development of PTDM. In a study of 173 consecutive patients, both multivariate linear regression analysis revealed a significant relationship between the 2-hour serum glucose level and the prednisolone dose. This study showed the risk of developing PTDM was 5% per 0.01 mg/kg/d of increase in prednisolone dose.[9] One meta-analysis that compared tacrolimus and cyclosporine found that insulin-dependent DM occurred in 9.8% of kidney transplant recipients on tacrolimus versus 2.7% of those on cyclosporine-based regimens.[10] Both calcineurin inhibitors cause reversible toxicity to islet cells and may directly affect transcriptional regulation of insulin expression. Sirolimus appears to be diabetogenic. Replacement of tacrolimus or cyclosporine with sirolimus was associated with a significant worsening rather than an improvement in insulin resistance.[2] It has also been shown that patients treated with tacrolimus and mycophenolate mofetil have lower rates of PTDM (14%) when compared to those taking tacrolimus and sirolimus (17%) or cyclosporine and sirolimus (33%).[11]

Posttransplant DM increases the risk of infection, sepsis, and cardiovascular disease,[12] and has adverse effects on the patient and graft survivals.[5,13] The increased relative risk of death due to cardiovascular disease ranges from 1.5 to 3 among those who develop PTDM versus those without DM.[3] Nearly, 10% to 20% of our transplant patients had a high plasma glucose after transplantation that showed a high rate of IGT and PTDM. All of our patients were CMV-antibody positive and HCV negative with a same ethnicity and protocol of treatment. The majority of our patients received a kidney from unrelated donors with several HLA mismatches. Therefore, we could not measure the effect of these factors on PTDM. In univariate analysis, recipient's age was a risk factor for PTDM (P = .02). Since the metabolic organ damage of diabetic patients generally appears 5 years after the onset of DM, we could not find a significant effect of PTDM on the 5-year patient and graft survival rates.

CONCLUSIONS

This study showed that DM after transplantation is a common metabolic disorder in our patients. We recommend a less diabetogenic immunosuppressive protocol, especially for our older recipients. A longer follow-up of a larger patient population helps us to better understand the risk factors and survival in our PTDM recipients.

CONFLICT OF INTEREST

None declared.

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