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Post-Transplant Diabetes Mellitus: Is It Associated With Poor Allograft Outcomes in Renal Transplants?

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ABSTRACT

Background. Post-transplant diabetes mellitus (PTDM) is a common metabolic complication whose incidence ranges from 2 to 50%, reflecting wide variations in population type, criteria for diagnosis, and immunosuppressive regimen. PTDM is associated with poor graft outcomes and increased infections and cardiovascular disease following renal transplants. Therefore, we assessed the incidence of PTDM and examined the association between PTDM and graft function after transplantation.

Materials and methods. We investigated 565 renal transplants in our center. The patients were divided into 2 groups, depending on the time of surgery: group 1 ($n = 228$, from January 1990 to December 1995) and group 2 ($n = 377$, from January 1996 to December 2011). In each group, patients were divided into no diabetes mellitus (non-DM), preexisting diabetes mellitus (pre-DM), and PTDM subgroups. PTDM was defined as fasting plasma glucose $\geq$126 mg/dL. We started treatment by modification of lifestyle and/or antidiabetic medication. All patients in group 1 received cyclosporine (CsA) and patients in group 2 received CsA or tacrolimus. We analyzed the clinical characteristics of recipients, serum creatinine levels, and long-term graft survival.

Results. The overall incidence of PTDM was 11.7% ($n = 66$); 9.2% ($n = 21$) in group 1, and 13.4% in group 2. There was a higher incidence of PTDM in the recipients who received tacrolimus than in those who received CsA (25.0% vs 9.5%, $P < .001$) and the delay before the appearance of PTDM was shorter (38.58 $\pm$ 6.94 vs 75.85 $\pm$ 7.67, $P = .017$). Also the tacrolimus dose (20.4l $\pm$ 4.28 ng/mL) at the time of PTDM diagnosis was above the therapeutic range (5–20 ng/mL). There were no significant differences in infection and cardiovascular complication rates between the non-DM, pre-DM, and PTDM patients in group 1. In group 2, the use of tacrolimus significantly increased the incidence of PTDM compared with CsA ($P < .001$). However, there were no significant differences between subgroups in other variables. Serum creatinine levels 10 years after renal transplantation ($P = .756$ in group 1 and $P = .559$ in group 2) and long-term graft survival in those groups were not significantly different ($P = .067$ in group 1 and $P = .125$ in group 2).

Conclusion. Renal function and allograft outcomes are more impaired in patients with PTDM than in either non-DM or pre-DM patients. However, if regular screening of plasma glucose levels, early diagnosis, and appropriate treatment of PTDM are carried out, the risk of complications can be minimized and the long-term allograft outcomes improved.

DIABETIC NEPHROPATHY is one of the major causes of end-stage renal disease (ESRD).[1,2] Patients with ESRD and diabetes mellitus (DM) have multiple comorbid complications, such as ischemic heart disease, congestive heart failure, and peripheral vascular disease.[3–5]

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These contribute to the high mortality and morbidity of patients with ESRD.[2,6] As a treatment, renal transplantation improves quality of life and increases survival, compared with long-term dialysis treatment.[6–9] However, pre-existing DM (pre-DM) leads to poor allograft outcomes and post-transplant DM (PTDM) also increases graft loss and decreases graft function.[6,10]

As a metabolic complication, PTDM is associated with increased risk of infection and cardiovascular disease, which are major causes of morbidity and mortality after renal transplantation.[3,8,11,12] The incidence of PTDM varies from 2 to 50%, and is influenced by various risk factors.[9,13,14] These include old age, obesity, high body mass index (BMI), family history, donor source, and ethnicity.[13,14] Both pretransplant risk factors and early post-transplant complications such as acute rejection, pretransplant comorbidity, delayed graft function, and viral or bacterial infection influence long-term graft function.[8,14,15] Also, the type and dose of immunosuppressive agent used to prevent and treat rejection influence the prevalence of PTDM.[8,14]

Negative impacts of PTDM on allograft function in renal transplants have been described in many studies. Therefore, we investigated the characteristics of donors and recipients at our center and compared the renal function and graft survival rates associated with pre-DM and PTDM to assess their clinical impact on renal function and long-term graft outcomes.

MATERIALS AND METHODS

Between January 1990 and December 2011, 565 renal transplants were performed in the Hanyang University Transplantation Center. The patients were divided into 2 groups according to the immunosuppressant used. Up to 1995, most patients received triple or dual therapy based on prednisolone, azathioprine, and cyclosporine (CsA). For most of the patients azathioprine was replaced by mycophenolate mofetil and CsA replaced by tacrolimus from 1996. Because of these changes in immunosuppressive therapy, patients were divided into 2 groups depending on the time of surgery: group 1 ($n = 228$, from January 1990 to December 1995) and group 2 ($n = 337$, from January 1996 to December 2011). There were also assigned to non-DM, pre-DM, and PTDM subgroups. The non-DM set included patients who were not diagnosed as DM before renal transplantation and showed no signs of DM after transplantation. In the pre-DM set were those who had been diagnosed with DM or had used an oral anti-DM medication or insulin therapy prior to renal transplantation. PTDM was diagnosed according to the American Diabetes Association guidelines using the criterion of fasting plasma glucose ≥l26 mg/dL.[2,8] These patients needed modification of lifestyle or antidiabetic or insulin therapy to normalize their blood sugar levels.

Baseline characteristics such as age, gender, BMI, human leukocyte antigens, hepatitis C status, hypertension, cardiovascular complications, and cerebrovascular accidents were collected from donors and recipients. Acute and chronic rejection, infection rates (viral, bacterial, and cytomegalovirus), and the use of CsA-based or tacrolimus-based immunosuppressant protocols were analyzed. Acute rejection was suggested by an unexplained rise in serum creatinine and percutaneous renal biopsy was performed to confirm acute rejection before starting antirejection therapy. Graft failure was defined as the need for dialysis, nephrectomy, or retransplantation. Infection was diagnosed on the basis of clinical symptoms, culture results, or serological markers as well as the need for treatment. To compare renal function and graft outcomes after renal transplantation, we checked serum creatinine levels at 6, 12, 36 months and 10 years after renal transplantation and analyzed long-term graft survival in each groups.

Patients characteristics were compared using the chi-squire test and Student t test and univariate and multivariate logistic regression analyses were carried out. The Kaplan-Meier method with log-rank tests was used to estimate graft survival. A Cox proportional hazard model was used to estimate associations between the groups. All analyses were performed using SPSS 18.0 and P values $<.05$ were considered statistically significant.

RESULTS

Of the total of 565 patients, 63 patients (11.2%) and 66 patients (11.7%) were diagnosed with pre-DM and PTDM, respectively. Baseline characteristics of the donors and recipients are presented in Table 1. The mean recipient age was 39.64 ± 10.75 (51–68) years and mean donor age was 39.47 ± 11.37 (16–66) years. There were more male than female recipients and donors ($n = 361$, 63.9% and $n = 315$, 44.2%). Only 33 renal transplants (5.8%) were from deceased donors. More recipients received CsA than tacrolimus ($n = 485$, 85.8% and $n = 80$, 14.2%). Acute and chronic rejection rates were 30.1% and 38.4%, respectively. The viral and bacterial, cytomegalovirus, and hepatitis C virus infection rates were 28.7%, 6.2%, and 1.4% respectively. Sixty-five patients (11.5%) developed cardiovascular complications and 23 (4.1%) experienced cerebrovascular accidents.

When we compared the incidence of PTDM according to the immunosuppressant used, the recipients who used tacrolimus were more susceptible than those who used CsA (25% [20/80] vs 9.5% [46/485], $P < .001$), and it took longer for PTDM to occur in the latter (75.85 ± 7.67 months vs 38.58 ± 6.94 months, $P = .017$). The tacrolimus level at the time of PTDM diagnosis (20.41 ± 4.28 ng/mL) was above its therapeutic range (5–20 ng/mL). All the patients received CsA-based immunosuppressant protocols until the end of 1995, after which we used tacrolimus instead of CsA. Therefore, we divided the patients into those transplanted prior to June 1996 (group 1) and those transplanted after that date (group 2), and we analyzed clinical characteristics, renal function, and graft outcomes in each group.

Among the 228 recipients who received renal transplants between January 1990 and December 1995 (group 1), 15 (6.6%) had pre-DM and 21 (9.2%) had PTDM. The others ($n = 192$, 84%) had no history of pre-DM or PTDM. The mean time until PTDM occurred was 88.28 ± 65.76 months after renal transplantation. In univariate analysis, older age of recipients ($P = .001$), more peritoneal dialysis ($P = .019$), and higher acute rejection rates ($P = .025$) were associated with development of PTDM. In multivariate analysis, older age, (hazard ratio [HR] = 1.113, 95% confidence interval [CI] 1.011–1.271, $P = .032$), more acute rejection