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CV: Cardiovascular

ESRD: End-stage renal disease

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Abstract

Background

Renal transplantation has been established as a treatment for end-stage renal disease (ESRD) due to diabetic nephropathy. However, few studies have focused on the outcome after renal transplantation in patients with ESRD and type 2 diabetic nephropathy. To investigate the effect of renal transplantation on ESRD with type 2 diabetic nephropathy, we retrospectively analyzed patients who received renal transplantation at our facility. This study aimed to compare the outcome of renal transplantation for type 2 diabetic nephropathy with that for non-diabetic nephropathy.

Methods

We studied 290 adult patients, including 65 with type 2 diabetic nephropathy (DM group) and 225 with non-diabetic nephropathy (NDM group), who underwent living renal transplantation at our facility from February 2008 to March 2013. We compared the two groups retrospectively.

Results

In the DM and NDM groups, the 5-year patient survival rates were 96.6% and 98.7%, and the 5-year graft survival rates were 96.8 and 98.0%, respectively, with no significant differences between the groups. There were no significant differences in the rates of surgical complications, rejection, and infection. The cumulative incidence of postoperative cardiovascular events was higher in the DM group than in the NDM group (8.5% vs 0.49% at 5 years; $P = .002$).

Conclusions

Patient and graft survival rates after renal transplantation for type 2 diabetic nephropathy are not inferior to those for recipients without diabetic nephropathy. Considering the poor prognosis of patients with diabetic nephropathy on dialysis, renal transplantation can provide significant benefits for these patients.

Introduction

Diabetic nephropathy is one of the complications of diabetes and is the main cause of end-stage renal disease (ESRD) worldwide. In Japan in 2012, 44.5% of new dialysis patients had diabetic nephropathy [1], most of whom had type 2 diabetes. Additionally, the 5-year survival rate of dialysis patients after the onset of dialysis, including all of the primary diseases, was 59.8% [1]. Furthermore, the risk of mortality of patients with diabetic nephropathy as a primary disease was 1.342 times higher than that of those with non-diabetic nephropathy [1], which represents a poor prognosis. Renal transplantation for patients with ESRD has an excellent prognosis compared with dialysis therapy and has become the most effective treatment. There are only a few studies on the results of kidney transplantation in patients with type 2 diabetes. Some of these studies have reported that the prognosis of patients with diabetic nephropathy after renal transplantation is poor compared with that of patients with non-diabetic nephropathy [2-4].

To investigate the effect of renal transplantation for ESRD with type 2 diabetic nephropathy, we conducted a retrospective analysis of patients who received renal transplantation at our facility. We compared the outcome of renal transplantation for type 2 diabetic nephropathy with that for non-diabetic nephropathy.

Materials and Methods

We studied a total of 290 patients, including 65 with ESRD and type 2 diabetic nephropathy (DM group) and 225 with ESRD and non-diabetic nephropathy (NDM group) who underwent living renal transplantation at our facility from February 2008 to March 2013. The demographics of the two groups are shown in Table 1. ESRD patients with type 2 diabetic nephropathy were defined as those with pre-existing diabetic retinopathy and diagnosed by a nephrologist. A comparative examination was performed retrospectively in the two groups to investigate the cumulative survival rate, the cumulative graft survival rate, surgical complications, rate of acute rejection, incidence of infection, and cumulative incidence of cardiovascular (CV) events after renal transplantation.

We performed the same immunosuppression protocol in both groups. Both groups were administered 20 mg of basiliximab on the day of the operation and 4 days after the operation. Oral immunosuppressive agents were

tacrolimus, mycophenolate mofetil, and methylprednisolone. ABO-compatible recipients in this study started these immunosuppression agents 7 days before the operation. For ABO-incompatible patients, oral immunosuppressants were administered from preoperative day 14 and 200 mg rituximab was administered on preoperative day 7.

Renal graft loss was defined as the time at which dialysis was reintroduced or retransplantation was performed. Surgical complications were defined as those that required reoperation. Acute rejection was diagnosed at a kidney biopsy, which was performed 3 months and 1 year after surgery according to protocol or whenever clinical rejection was suspected. Acute rejection was diagnosed based on the Banff [5] classification in view of the clinical course and biopsy findings. All of the specimens were evaluated by two experienced pathologists (A. Tsuchimoto and K. Masutani) using a dual light microscope. When a patient was diagnosed with acute rejection, treatment based on the following strategies was conducted. For acute T-cell rejection, steroid-pulse therapy was performed for 3 or 7 days depending on the grade of rejection and the patient's condition, such as infection or previous disease. For steroid-resistant rejection, patients were treated with antithymocyte globulin. When a patient was diagnosed with acute antibody-mediated rejection, the patient was treated by plasma exchange and gamma-globulin administration. Infection was defined as clinical symptoms and the need for hospitalization. In accordance with the report of Cosio et al. [6], pre- and post-transplant CV diseases were defined as follows: (i) onset of acute myocardial infarction and/or the need for percutaneous or surgical revascularization; (ii) need for amputation of a limb and/or revascularization due to arteriosclerosis obliterans; and (iii) onset of stroke. The cumulative patient survival rate/graft survival rate, surgical complications, infection/acute rejection throughout follow-up, and post-transplant cumulative CV events were analyzed to investigate the contributing risk factors.

Patients were followed up until 30 June 2014. JMP Pro 11 (SAS Institute, Cary, NC, USA) was used for statistical analysis. The cumulative patient survival rate/graft survival rate, surgical complications, infection/acute rejection throughout follow-up, and post-transplant cumulative CV events were analyzed. The Kaplan–Meier method was used to calculate the cumulative patient survival/graft survival rate and the log-rank test was used for testing the difference. Multivariate analysis was performed using the Cox proportional hazards model to identify the risk factors for comparing the prognosis after correcting for deviation of the patient's background. The χ^2 test was used for testing background factors and the Wilcoxon test was used to determine whether the difference

between the two groups was statistically significant. $P < .05$ was defined as significant for all of the statistical analyses.

Results

Table 1 shows the patients' clinical characteristics. The mean age and the male to female ratio in the DM group were higher than those in the NDM group ($P < .001$, $P = .004$, respectively). The percentage of patients with preemptive renal transplantation in the DM group was lower than in the NDM group ($P = .033$). The morbidity of pre-transplant CV diseases was significantly higher in the DM group than in the NDM group ($P < .001$). No significant differences were found in ABO-incompatible transplantation, the pre-transplantation dialysis period, the donor's age, and the follow-up period between the two groups.

The cumulative survival rates in the DM and NDM groups were 98.5% and 99.1% for 1 year, and 96.6% and 98.7% for 5 years, respectively (Figure 1A), with no significant differences between the groups. There were two deaths in the DM group and three deaths in the NDM group during the observation period. In the DM group, one of the fatalities was due to brain hemorrhage and another was due to infection (tuberculosis). In the NDM group, all of the fatalities were caused by infection (sepsis, hepatitis B, and cytomegalovirus).

The death-censored cumulative graft survival rates in the DM and NDM groups were 100% and 99.1% for 1 year and 96.8% and 98.0% for 5 years, respectively (Figure 1B), with no significant differences between the groups. There were two cases of renal graft loss in the DM group, excluding the fatal cases. One renal graft loss was due to BK virus nephropathy and the other was caused by adenovirus infection. In the NDM group, four cases of renal graft loss were observed. One renal graft loss was due to recurrent nephritis, one was due to BK virus nephropathy, and the remaining two were due to acute rejection induced by infection.

The incidence of surgical complications ($P = .86$) acute rejection ($P = .30$), and infection ($P = .55$) was not significantly different between the DM and NDM groups (Table 2).

The 5-year cumulative incidence of post-transplant CV events was significantly higher in the DM group than in the NDM group (8.5% vs 0.49%, $P = .002$, Figure 2). In the DM group, four cases of post-transplant CV events occurred and the mean onset period was 17.3±15.4 months. One patient died of a brain hemorrhage and another

three needed lower limb amputation or revascularization because of arteriosclerosis obliterans. One case of a post-transplant CV event developed in the NDM group. This patient required percutaneous transluminal coronary angioplasty due to angina at 18 months post-transplant. The Cox proportional hazards model was used for analysis of post-transplant CV events. Table 3 shows the risk factors during the entire observation period. Only DM showed a significant difference in univariate and multivariate analyses, and was considered to be an independent risk factor for CV events after renal transplantation.

Discussion

According to the statistical data of the Japanese Society for Dialysis Therapy, the 5-year survival rate of dialysis patients after the onset of dialysis, including all of the primary diseases, is 59.8% [1]. Additionally, the 5-year survival rate of patients with diabetic nephropathy as a primary disease is estimated to only be 50% [1]. Type 2 diabetes is increasing on a global scale. However, few studies have focused on the outcome after renal transplantation in patients with ESRD and type 2 diabetic nephropathy.

In this study, we showed that the 5-year cumulative survival rate after renal transplantation was excellent (96.6%). There was no significant difference in the outcome of renal transplantation between the DM and NDM groups. Additionally, univariate and multivariate analysis showed that DM had no significant effect on patient and graft survival rates.

Although onset/progression of infection and the risk of death from infection are increased in patients with diabetes [7], our study showed no significant difference in the incidence of infection that might need hospitalization between the two groups. Most of the infections in both groups were caused by viruses, such as cytomegalovirus, herpes zoster, and adenovirus. Urinary tract infection is more common in diabetic than in non-diabetic transplant recipients [8-9]. However, in our patients, urinary tract infection was not observed in the DM group.

CV events are the primary cause of death in diabetic patients after renal transplantation. CV events account for 50–80% of mortality in all diabetic patients, and are often observed within 3 months after renal transplantation [6]. Based on these facts, some studies have reported that the prognosis of patients with diabetic nephropathy after renal transplantation is poor compared with that of patients with non-diabetic nephropathy [10-12]. Although the

incidence of post-transplant CV events was significantly higher in the DM group than in the NDM group, only one patient died of a brain hemorrhage and no patients died of coronary artery disease in either group. As a result, CV events did not cause a significant difference in survival between the groups. The prevalence of coronary artery disease in asymptomatic diabetic patients who are evaluated for renal transplantation is 33–50% [13]. Therefore, pre-operative screening among diabetic renal transplantation candidates should be routinely performed. One reason why we achieved a good outcome in the DM group is that at our facility, all of the patients underwent pre-transplant echocardiography, drug-induced stress myocardial perfusion scintigraphy, and an examination by a cardiologist. The similar prognosis in the DM and NDM groups might be explained by the fact that deaths due to coronary artery disease in the early post-transplant period could be subsequently prevented. Another reason for the good outcome is that diabetologists managed glycemic control in all of the diabetic patients in the peri- and postoperative periods. Poor glycemic control induces macrovascular complications and shortens the survival of these patients. Moreover, in renal transplant recipients, a high HbA1c level is a predictor of mortality and graft failure [14]. Therefore, careful attention to glycemic control for diabetic patients undergoing renal transplantation can also be expected to improve graft survival in addition to prevention of CV events.

Conclusion

This study shows that patient and graft survival rates after renal transplantation in patients with type 2 diabetic nephropathy are not inferior to those with non-diabetic nephropathy over 5 years. Considering the poor prognosis of patients with diabetic nephropathy after the onset of dialysis, performing renal transplantation for ESRD in patients with type 2 diabetic nephropathy is beneficial. The incidence of post-transplant CV events was significantly higher in the DM group than in the NDM group, which indicates that intensive diabetic control and attentive care of CV diseases are required for an acceptable long-term outcome.

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Table 1. Clinical characteristics

Characteristics	DM group ($n = 65$)	NDM group ($n = 225$)	*P*
Recipient's age (years)[a]	54.5±9.9	43.6±14.1	<.001
Recipient's sex (male:female)	48:17	121:104	.004
ABO-incompatible, n (%)	24 (36.9)	67 (29.9)	.28
Preemptive transplants, n (%)	9 (13.9)	60 (26.7)	.033
Months on dialysis pre-transplant[a]	29.3±34.2	52.1±68.4	.38
Pre-transplant CV events, n (%)	18 (27.7)	16 (7.1)	<.001
Donor's age (years)[a]	53.1±13.5	56.8±10.2	.051
Follow-up (months)[a]	36.8±16.3	39.2±17.2	.32

CV, cardiovascular; DM, type2 diabetic nephropathy; NDM, non-diabetic nephropathy.

[a]Values reported as mean ± standard deviation.

Table 2. Clinical outcome of the patients

	DM group ($n = 65$)	NDM group ($n = 225$)	*P*
Surgical complications, n (%)	2 (3.08)	6 (2.67)	.86
Acute rejection, n (%)	15 (23.1)	39 (17.4)	.30
Infection, n (%)	12 (18.5)	49 (21.9)	.55

DM, type2 diabetic nephropathy; NDM, non-diabetic nephropathy.

Table 3. Analysis of risk factors for post-transplant CV events

Univariate analysis	**HR**	**CI**	***P***
DM	14.40	2.13–281.63	.006
Recipient's age	1.08	1.01–1.19	.032
Male sex	1.05	0.17–7.94	.96
Preemptive transplants	0.89	0.05–6.07	.92
ABO-incompatible	1.51	0.20–9.12	.66
Donor's age	0.98	0.91–1.06	.53
Months on dialysis pre-transplant	1.00	0.99–1.01	.53
Pre-transplant CVD	1.88	0.10–12.71	.60
Rejection	0.97	0.05–6.58	.98
Infection	2.38	0.31–14.39	.36
Multivariate analysis	**HR**	**CI**	***P***
DM	36.50	2.74–1869	.005
Recipient's age	3.24	0.46–29.89	.24
Male	1.08	0.12–10.97	.94
Preemptive transplants	2.80	0.11–33.42	.46
ABO-incompatible	0.91	0.10–7.04	.93
Donor's age	1.01	0.93–1.09	.85
Months on dialysis pre-transplant	1.02	1.0–1.03	.09
Pre-transplant CVD	0.66	0.03–5.95	.74
Rejection	0.87	0.04–8.57	.91
Infection	3.08	0.27–34.37	.34

CI, confidence interval; CVD, cardiovascular disease; DM, type2 diabetic nephropathy; HR, hazard ratio.

Fig. 1A. Patients' survival rates.

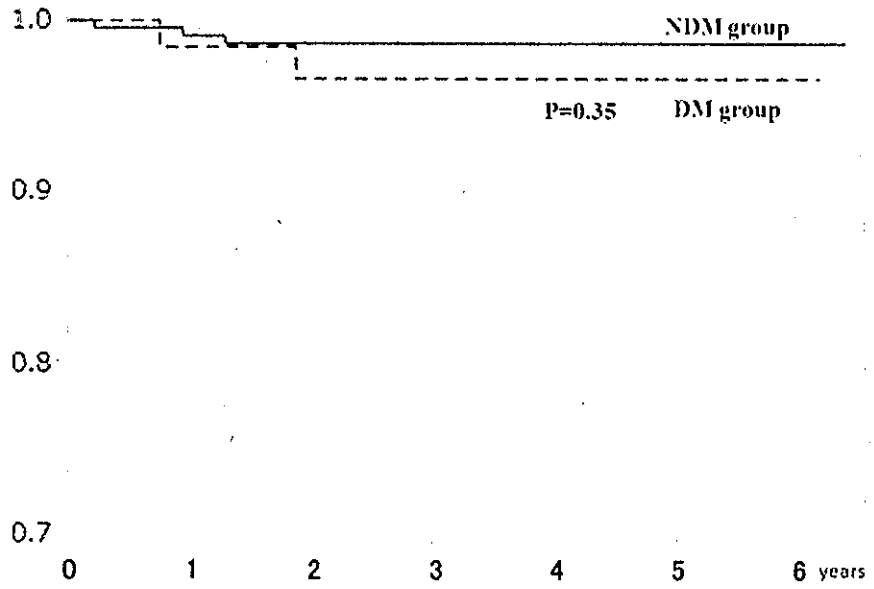

Fig. 1B. Death-censored graft survival rates.

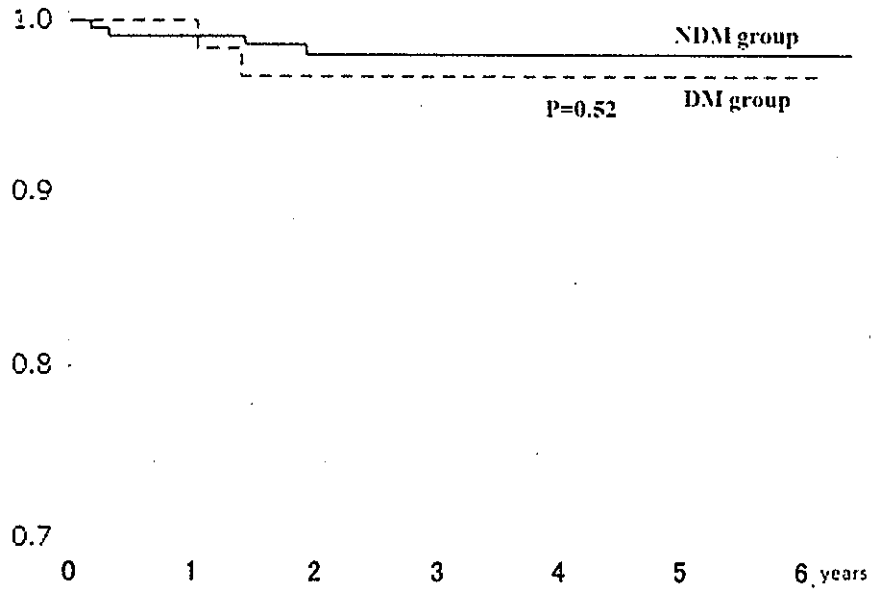

Fig. 2. Cumulative post-transplant CV events.