Inferior Long-Term Outcome of Renal Transplantation in Patients with Diabetes mellitus

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Key Words

Diabetes mellitus · Kidney transplantation, complications, outcome

Abstract

Objective: To retrospectively review the long-term outcome of renal transplant in diabetics at Mubarak Al-Kabeer Hospital and Hamad Al-Essa Organ Transplant Center, Kuwait from 1983 to 1998. **Methods:** There were 631 renal transplant patients, comprising 79 (12.5%) patients with pretransplant diabetes mellitus (pre-TDM), 117 (18.5%) patients with post-transplant diabetes mellitus and 435 (69%) nondiabetics (ND). Subjects with post-transplant diabetes mellitus were excluded from the comparative analysis. Distribution of sex, source of donors and mode of immunosuppression were similar in pre-TDM and ND groups. **Results:** Fifty-three (67%) recipients in pre-TDM and 90 (20.5%) in the ND group ($p < 0.01$) were above 45 years of age. However, 26 (33.3%) pre-TDM and 345 (79.5%) ND were below age 45. Among those who died, coronary artery disease led to death in 36% of pre-TDM and 27% in ND. Hyperlipidemia requiring drug therapy was observed in 37% pre-TDM and 6% ND. The incidence of severe infections was nearly twice

in pre-TDM over ND recipients (1.9 vs. 1.0 per patient, $p < 0.001$). Acute rejection episodes were more frequently seen in pre-TDM (43%) than ND (33%), however the difference was not statistically significant. The patient survivals at 1, 5, 10, 14 years were significantly lower in pre-TDM (84, 65, 58 and 58%, respectively) than in ND (97, 93, 86 and 82%, respectively). The major contributory factors were severe infections and coronary artery disease. The cumulative graft survival showed a similar pattern (52% in pre-TDM, 73% in ND at 10 years). However, when death is excluded, the 10-year pure graft survival probability was similar for the pre-TDM and ND groups (76% vs. 80%). **Conclusion:** Our study indicates poor patient survival in pre-TDM due to coronary artery disease and infections, whereas the pure long-term graft survival was equally good in pre-TDM and ND transplant recipients.

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Introduction

Diabetics represent the largest single category of new patients receiving end-stage disease care in many countries [1]. In contrast to the 1970s when chronic diabetics

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were rarely accepted for any form of renal replacement therapy, they are now regularly accepted for all types of renal replacement therapy. The survival rate of uremic diabetic patients treated with chronic hemodialysis was extremely poor compared to those who had kidney transplantation and nondiabetic dialysis patients [2–5]. However, with improvements in hemodialysis, transplantation and advent of chronic ambulatory peritoneal dialysis, 1-year survival of uremic diabetics has increased to 70% [6]. This improvement in patient survival has spurred transplant centers to accept more diabetics for renal transplantation.

Outcome of renal transplantation in patients with pre-transplant diabetes mellitus (pre-TDM) compared to that of nondiabetics (ND) is still debated. Because of the significant morbidity and mortality clinicians doubted the success of transplantation in uremic diabetics [7]. Some centers have reported higher mortality and lesser patient and graft survivals in diabetics compared to ND [7, 8]. However, other authors have found similar patient and graft survival in both these groups [7–12]. This prompted us to review our experience with transplantation in uremic diabetics and compare it with that in ND.

Subjects and Methods

During the period from 1983 until 1998, 631 renal transplant recipients were followed up in the Nephrology Unit of Mubarak Al-Kabeer Hospital and Hamad Al-Essa Organ Transplant Center in Kuwait. These patients received 640 grafts and included 79 (12.5%) patients with pre-TDM, 117 (18.5%) with post-transplant diabetes mellitus (PTDM) and 435 (69%) ND. The pre-TDM group included 32 with type 1 and 47 with type 2 diabetes mellitus. Subjects with PTDM were excluded from the present study to avoid influence of results by effect of PTDM. In addition to information on age, sex, donor type, immunosuppressive therapy, dialysis, primary renal disease, details of rejection episodes and infections, graft and patient outcome were also collected by retrospective review of hospital records. In this study data on the pre-TDM group was then compared with that in ND recipients. Acute rejection is defined as an immediate deterioration of allograft function that is associated with specific pathologic changes in the renal allograft. While chronic rejection is slowly progressive allograft dysfunction, which occurs after the 1st year of transplantation, associated with proteinuria and variable histological renal allograft changes involving blood vessels, glomeruli, interstitium and tubules.

Immunosuppressive Therapy and Prophylaxis

Most renal transplant recipients were on triple-drug immunosuppression with prednisolone (1 mg/kg tapered to 10 mg/day in 6 months), cyclosporin A (7 mg/kg/day tapered to 1–2 mg/kg/day in 6 months) and azathioprine (1–1.5 mg/kg tapered to 1 mg/kg/day in 6 months). Monoclonal anti-T-cell antibody (OKT3) and antilymphocyte globulin were not used in the induction protocol. Intrave-

Table 1. Demographic features of subjects with pre-TDM and of ND

	Pre-TDM		ND	
	n	%	n	%
<i>Sex</i>				
Male	47	59.5	287	66
Female	32	40.5	148	34
<i>Age, years</i>				
<30	6	8	147	33.8
31–45	20	25.3	198	45.5
46–60	39	49.4	76	17.5
>61	14	17.3	14	3.2
<i>Nationality</i>				
Kuwaiti	62	78.5	235	54
Non-Kuwaiti Arabs	15	19	147	33.8
Others	2	2.5	52	12.2
<i>Primary renal disease</i>				
Diabetic nephropathy	52	65.8	–	–
Chronic glomerulonephritis	7	8.9	157	36.1
Chronic tubulointerstitial disease	13	16.5	163	37.5
Hereditary renal disease	3	3.8	20	4.6
Hypertensive nephrosclerosis	1	1.2	11	2.5
Others	3	3.8	84	19.3

nous methylprednisolone pulses and/or OKT3 were used in the treatment of rejection episodes. All patients had prophylactic oral nystatin, trimethoprim-sulfamethoxazole and acyclovir regularly for the first 6 months after transplantation.

Statistics

Fisher's exact test was used to compare differences in groups for significance. Survivals were done using life table and log rank statistics was used for determining differences between two actual survival rates. Differences were considered significant if p value was <0.05.

Results

Demographic features of patients in pre-TDM and ND groups are shown in table 1. While 79% of ND were below the age of 45 years, 67% of pre-TDM were above 46 years, showing that diabetic recipients are older. The majority (78%) of pre-TDM recipients were local nationals. Table 2 shows details of pretransplant dialysis and type of donors. Preemptive transplants were more common in ND (23%) compared to pre-TDM (11%) recipients. Even though live related donors were more frequent in ND recipients and live unrelated donors in pre-TDM, the differences were not significant. Live unrelated donors in

Table 2. Pretransplant dialysis and type of donor

	Pre-TDM		ND	
	n	%	n	%
Preemptive	9	11.4	101	23.2
<i>Dialysis</i>				
Hemodialysis	56	70.9	308	70.8
Peritoneal dialysis	14	17.7	26	6.0
<i>Donor</i>				
Live related	25	31.6	202	45.9
Live unrelated	48	58.2	202	45.9
Cadaver	8	10.2	36	8.2

Table 3. Immunosuppression used in patients with pre-TDM and ND recipients

Drugs	Pre-TDM		ND		p
	n	%	n	%	
Pred + CyA	5	6.3	17	3.9	
Pred + CyA + azathioprine	69	87.3	328	75.8	
Pred+ CyA + mycophenolate	1	1.3	14	3.2	
	75	94.9	359	82.9	NS
Pred alone			1	0.2	
Pred + azathioprine	4	5.1	73	16.9	
	4	5.1	74	17.1	NS

NS = Not significant; Pred = prednisone; CyA = cyclosporin A.

Table 4. Post-transplant major nonimmunologic complications

Complications	Pre-TDM	ND
Infection (episodes requiring hospitalization)		
Bacterial	113	391
Fungal	21	24
Mycobacterial	7	9
Viral	9	33
Infections per patient	1.9	1.0
Coronary heart disease	28	26
Cerebrovascular stroke	3	3
Peripheral vascular disease	5	–
Hyperlipidemia	29	25
Malignancy	7	8
Blindness	2	–

pre-TDM and ND groups were spouses (14 and 48), friends (14 and 68) and other emotionally related persons (20 and 86), respectively. Immunosuppression used in these recipients is shown in table 3. There is no difference in the percentage of subjects receiving cyclosporin A including other immunosuppressants between pre-TDM and ND groups.

Major nonimmunological post-transplant complications are shown in table 4. Incidence of significant infections requiring hospitalization was higher in recipients with pre-TDM than in ND throughout the period of follow-up. The localization of the infections in pre-TDM and ND recipients were septicemia (38 and 110), pneumonia (31 and 112), urinary tract (39 and 132), cutaneous abscess (13 and 10), gastrointestinal (4 each), hepatitis (2 and 3), meningitis (1 and 2), wound infection (9 and 42) and others (13 and 42), respectively. Similarly cerebrovas-

Table 5. Causes of death

Cause	Pre-TDM		ND		p
	n	%	n	%	
Infections	14	56	20	48.9	NS
Coronary heart disease	9	36	11	26.8	<0.001
Cerebrovascular stroke	1	4	4	9.8	NS
Malignancy	–	–	3	7.3	–
Liver-related	–	–	1	2.4	–
Surgery-related	1	4	2	4.9	NS
	25/79	31.6	41/435	9.4	<0.001

NS = Not significant.

Table 6. Causes of graft loss in patients with pre-TDM and ND

Cause	Pre-TDM		ND		p
	n	%	n	%	
Accelerated rejection	–	–	2	3	
Acute rejection	5	17.2	11	16.4	NS
Chronic rejection	7	24.1	32	47.8	NS
Recurrent renal disease	–	–	2	3	NS
Surgical causes	1	3.4	4	6	NS
Died with functioning graft	16	55.2	16	23.9	<0.001
	29/79	36.7	67/440	15.2	<0.05

NS = Not significant.

cular accidents (stroke) and coronary heart disease were observed more significantly more often in pre-TDM recipients. Peripheral vascular disease requiring amputation occurred only in recipients with pre-TDM. We also observed a higher prevalence of malignancies in the pre-TDM recipients. Three subjects developed recurrence of diabetic nephropathy in renal allografts.

Causes of death in 25 recipients with pre-TDM and 41 ND are shown in table 5. Patient mortality was significantly higher in pre-TDM ($p < 0.001$). Even though infections formed a major cause of mortality in both groups, death due to coronary artery disease was significantly higher among pre-TDM recipients ($p < 0.001$). During the follow-up period 29 grafts were lost in pre-TDM and 67 in the ND groups ($p < 0.05$, table 6). Death with functioning graft formed the major and significant cause of graft loss in the pre-TDM group ($p = 0.001$). Table 7 shows cumulative patient and graft survival in both groups. Recipients in the pre-TDM group had significantly lower survival

Table 7. Cumulative patient and graft survival (%)

Year	Pre-TDM	ND	p
Patient survival			
1	84	97	<0.01
5	65	93	<0.0001
10	58	86	<0.0001
14	58	82	<0.0001
Graft survival			
1	85	95	<0.05
5	65	88	<0.0001
10	52	73	<0.0001
14	52	61	<0.01
Censored graft survival			
1	93	97	NS
5	85	91	NS
10	76	76	NS
14	76	72	NS

NS = Not significant.

showing the increased risk of mortality in pre-TDM compared to ND recipients.

The cumulative graft survival was significantly less in recipients with pre-TDM compared to ND (table 7). But censored graft survivals were not different between these groups (table 7). This showed the impact of dying with functioning graft in graft survival in recipients with pre-TDM.

Discussion

Over the past few years, there has been a growing tendency to perform kidney transplants on diabetic patients, thereby providing renal care personnel more information and experience in taking care of these patients [9]. Vascular disease is probably the major contributing factor to patient morbidity and mortality following transplantation in diabetic recipients [10, 11]. In a 5-year survival of diabetic renal allograft recipients, diabetic patients without vascular disease (79%) had a significantly higher survival rate than those with vascular disease (8%) [13]. Other major factors associated with a higher incidence of cardiac death are hyperlipidemia, hypertension and extra-renal microangiopathy. Significant coronary artery disease, peripheral vascular disease and stroke could have definitely contributed to higher mortality in our diabetic recipients. Previous studies mainly concentrated on progression of vascular disease as a cause of higher mortality in diabetic recipients. Our findings are consistent with these reports. In addition, our data also indicate that infection is a contributing factor, although it also occurred at a similar rate in ND recipients.

There are varying reports on long- and short-term survival rates of diabetic recipients compared to those of ND [7, 10, 12–14]. While Eckberg and Christensson [7] and Shaffer et al. [13] reported similar rates, in the present study, pre-TDM had lower survival rates than ND. The probable explanation is that many elderly patients with occult diabetic vascular complications were included in the pre-TDM group. We recommend reduction of cardiovascular risk factors and subsequent better cardiovascular management as measures to improve patient survival in uremic diabetic patients. Recently, calcium channel blockers have been shown to improve both patient and graft survival in diabetic recipients [15].

Death of patients with functioning graft was the major cause of graft loss in pre-TDM recipients in this study. Similar observations were made earlier where two thirds of graft loss were due to patient death [13]. Other causes

of graft loss were similar in pre-TDM and ND recipients throughout the period of follow-up. Hence it can be presumed that pre-TDM or its milieu has no direct impact on the graft itself.

Conclusion

Recipients with pre-TDM have increased mortality mainly due to cardiovascular complications. This is also accompanied by inferior patient and graft survival after transplantation compared with ND. Patients dying with functioning graft continue to be the reason for inferior graft survival in pre-TDM recipients. We recommend screening of diabetics with end-stage renal disease carefully for vascular disease and avoiding transplantation in those who are found to have advanced disease for improving survival in diabetic patients with end-stage renal disease. Even with this type of screening, transplantation and follow-up in diabetic uremics will still remain a challenge.

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