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Similar treatment success rate after renal transplantation in diabetic and nondiabetic patients due to improved short- and long-term diabetic patient survival

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Abstract In the early era of transplantation, it was common practice to exclude diabetic patients since the outcome in such cases was usually poor. At our center in Malmö, Sweden, diabetic nephropathy was never regarded as a contraindication. During the 22-year period from 1972 to 1993, 223 renal allografts were transplanted in 189 uremic diabetics, representing 24 % of all renal transplant recipients (n = 788). The two subgroups – patients with and without diabetes – did not differ significantly in graft survival rates for the 22-year period, which was characterized by a successive improvement in the success rate that was especially striking in the diabetic nephropathy subgroup. Among transplantations performed before 1988, the overall patient survival rate was significantly lower in the diabetic subgroup than in the remainder. After 1988 (when a series of new procedures had been adopted), the patient survival rate in the diabetic subgroup was similar to that in the nondiabetic subgroup, a similarity that persisted for at least 5 years. The 1st year post-transplant mortality rate was reduced in diabetic patients from 24 % before 1988 to 0 % in those transplanted after 1988. In the 22-year period as a whole, cardiovascular or cerebrovascular events were the most common cause of death in both subgroups; the risk of cardiovascular or cerebrovascular death was reduced after 1988, and the rates were similar in both subgroups. The improved success rate of renal transplantation in patients with diabetic nephropathy supports continuation of the renal transplant program, which is based on careful management of the early stages of the disease.

Key words Kidney transplantation in diabetics · Diabetics, kidney transplantation · Graft survival, kidney transplantation, diabetics

Introduction

Diabetic nephropathy is one of the most common causes of end-stage renal failure in the Western world [24], currently accounting for 25 %–30 % of cases scheduled for active treatment of terminal uremia [21, 23]. In the past, however, diabetic patients tended to be excluded from end-stage renal failure programs because of the presence of other severe complications. Owing to the adverse effects of corticosteroids and significant post-transplant morbidity and mortality, clinicians doubted that renal transplantation in diabetic recipients would be successful. One important risk factor has been the high prevalence of coronary artery disease among diabetics [3, 12]. Therefore, at many centers the presence of diabetes was considered a contraindication for renal transplantation. However, the survival rate of uremic diabetic patients treated with chronic hemodialysis was extremely poor compared to that among nondiabetic dialysis patients [4] and inferior to that after transplantation [14, 16, 18].

Accordingly, transplantation continued to be performed in some diabetic patients, although the outcome was worse for diabetic than for nondiabetic patients [11, 14]. During the 1970s, however, results consistently improved [22], and diabetic patients were increasingly accepted for transplantation, a trend that was particularly striking in Sweden. In the mid-1980s, the 1-year patient survival rate after kidney transplantation was demonstrated to be similar in diabetic and nondiabetic patients [6, 22, 23], though other reports from this time showed the 5-year patient survival rate to be poorer in diabetics [12, 19]. Recently, a study of recipients transplanted during the period 1987–1993 demonstrated 5-year rates for both patient and graft survival that were not significantly different in diabetic and nondiabetic patients [21].

The Transplant Unit at Malmö was one of the first centers in Scandinavia to accept diabetic patients for renal transplantation, and our interest in transplantation among diabetic patients has remained strong. We now report on the evaluation of results obtained among diabetic patients who received renal allografts during a 22-year period. The continued development in the management of diabetes mellitus and of transplantation is reflected in the improved outcome after renal transplantation in cases of diabetic nephropathy.

Patients and methods

During the period 1972 through 1993, 957 renal transplantations were performed on adult patients (≥15 years old) at the Transplant Unit at Malmö University Hospital, Malmö, Sweden. A total of 223 (23%) of these grafts went to 189 diabetic patients and 734 went to 599 nondiabetic patients. The median duration of follow-up in surviving patients was 8 years, with a minimum of 22 months. Another 20 diabetic patients underwent combined renal and pancreatic transplantation and were not included in this study.

During this 22-year period, several changes in the clinical management improved the overall results. In 1983, cyclosporin A (CyA) was introduced, followed by the use of lower doses of corticosteroids, and triple immunosuppression, including azathioprine (Aza), became the standard treatment. Since 1988, when the brain-death criterion was adopted in Sweden, all cadaver kidneys have been harvested from heart-beating donors. At the same time, antibody (antithymocyte globulin and OKT3) antirejection treatment and prophylaxis were also introduced, and the use of ultrasonography for screening graft pathology and for biopsy guidance became clinical routine. Thus, as the clinical protocol has been uniform at our center since 1988, this date may be used to divide the study period into two separate parts.

Mean age at first transplantation was lower in the diabetic than in the nondiabetic subgroup (38 ± 9 vs 46 ± 13 years; $P < 0.001$). The overall proportions of living related donor (LRD) transplants and retransplants were 23% and 19%, respectively. Throughout the study period, LRD transplants were more frequent in the diabetic than in the nondiabetic subgroup (33% vs 19%; $P < 0.001$; Table 1). Retransplantation was of similar overall frequency in the two subgroups, though it tended to be less frequent in the diabetic subgroup during the study period 1988–1993, (15% and 21%, respectively; $P = 0.06$).

Among patients who received transplants since 1988, there were no significant differences between diabetic and nondiabetic recipients with regard to the mean number of mismatches (2.5 vs 2.9), the average length of cold ischemia time (17.6 vs 16.2 h), or the proportion of patients with at least one episode of acute rejection (52% vs 61%).

The current clinical protocol, used since 1988, includes triple immunosuppression with CyA, Aza, and prednisolone (Pred). LRD graft recipients receive medication for 2 days prior to transplantation and cadaveric donor (CD) graft recipients receive a single oral dose preoperatively. At the start of surgery, 500 mg methylprednisolone is given i.v. Postoperative immunosuppression includes CyA, initially at 10 mg/kg per day, and then decreased according to the patient's whole blood trough levels, Aza 1.5–2 mg/kg per day, and Pred tapered from 100 mg/day to 20 mg/day for the first 8 days. Rejection is treated with pulse-dose administration of methylprednisolone, 500 mg the first day followed by 250 mg/day for 3 days. In steroid-resistant rejection episodes, antibody antirejection treatment is given. In cases of histologically verified vascular rejection and positive repeated crossmatch, plasmapheresis or protein A immunoadsorption is considered.

Prior to inclusion on the waiting list or scheduling for LRD transplantation, all recipients are examined by the referring nephrologist and reviewed by the transplant surgeon. Additional examinations are performed on all diabetic transplantation candidates and include a thorough clinical examination, especially with regard to cardiovascular status. A thallium stress test is performed, and if reversible myocardial ischemia is present, coronary angiography is carried out to check for possible significant coronary artery stenoses.

Both patient and graft survival were evaluated using the Kaplan-Meier life-table technique with log rank statistics. Graft survival was analyzed in two ways for patients who died with a functioning graft. First, analyses were censored for these events, and second, they were regarded as graft loss. Below, the first definition is current if not otherwise stated. For multivariate analyses of graft survival, the Cox proportional hazard model was used. The risk of patient death due to cardiovascular or cerebrovascular disease was analyzed using the Kaplan-Meier life-table technique with terminal event defined as death from this cause. Patient survival analyses included patient data from primary transplantation only in order not to add repeated survival data from patients receiving a retransplant. The chi-square test and Student's t-test were used, as appropriate, to compare group data.

Results

During the study period as a whole (1972–1993), the diabetic subgroup was characterized by significantly shorter overall patient survival (from the first transplantation onwards; $P < 0.001$; Fig. 1a) and clearly a higher risk of death in the 1st postoperative year. The diabetic and nondiabetic subgroups did not differ significantly in overall graft survival (Fig. 1b), and there was a manifest risk of graft loss during the 1st postoperative year in both subgroups.

To evaluate changes over time for the diabetic patients, the data for this subgroup were split into three time periods according to date of transplantation (Fig. 2). CyA was introduced in 1983, and since 1988 heart-beating donors and antibody antirejection

Table 1 Transplantation data of diabetic and nondiabetic patients who received one or more renal allografts during the period 1972–1993 (*LRD*, living related donor)

	Diabetics		Nondiabetics		Total	
	n	[%]	*n*	[%]	*n*	[%]
1972–1987						
Recipients	144		363		507	
Transplants	175		451		626	
First transplants	144		363		507	
Retransplants	31	(18)	88	(19)	119	
LRD transplants	47	(27)	75	(17)*	122	
1988–1993						
Recipients	47		270		317	
Transplants	48		283		331	
First transplants	41		223		264	
Retransplants	7	(15)	60	(21)	67	
LRD transplants	27	(56)	68	(24)**	95	
1972–1993						
Total recipients	189		599		788	
Total transplants	223		734		957	
Total first transplants	185		586		771	
Total retransplants	38	(17)	148	(20)	186	(19)
Total LRD transplants	74	(33)	143	(19)**	217	(23)

* $P < 0.01$; ** $P < 0.001$ for differences in frequency of LRD or retransplantation in nondiabetic vs diabetic patients

Table 2 Comparison of outcome in terms of patient survival and graft survival in diabetic and nondiabetic patients after renal transplantation during the 22-year period, 1972–1993, stratified for donor type and primary or retransplantation (*LRD*, living related donor; *CD*, cadaveric donor)

Transplant	Patient survival[a] *P* value	Graft survival[b] *P* value
LRD	< 0.001	NS
CD	< 0.001	NS
First	< 0.001	NS
Second or more	< 0.01	NS
First LRD	< 0.001	NS
First CD	< 0.001	NS
Second CD	< 0.01	NS

[a] Patient survival was consistently better in the nondiabetic subgroup

[b] Graft survival did not differ significantly between diabetic and nondiabetic patients

treatment have been routinely used. Both patient (Fig. 2a) and graft (Fig. 2b) survival increased markedly for each time period, the improvement in patient survival being especially striking.

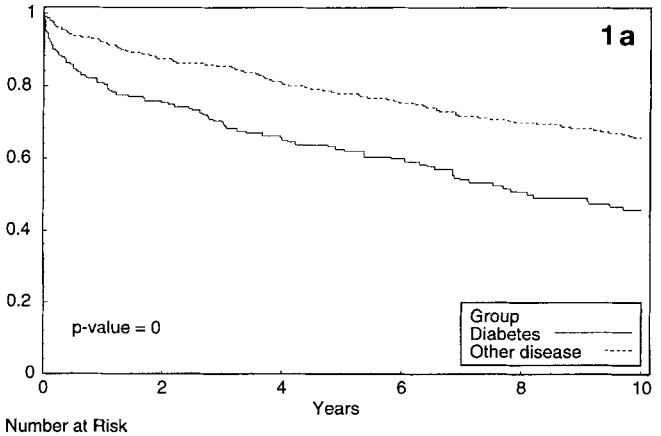
Further comparison of subgroup data for the two periods 1972–1987 and 1988–1993 showed outcome in terms of patient survival to be significantly poorer in the diabetic subgroup during the first period ($P < 0.001$; Fig. 3a) but not after 1988 (Fig. 3b). Corresponding analysis of graft survival showed that the diabetic and nondiabetic subgroups did not differ significantly in this respect either before or after 1988 ($P = 0.6$ and $P = 0.2$, respectively).

To exclude the possibility that the similarity in graft survival in the two subgroups might have been due to a higher proportion of LRD or primary transplants in the diabetic subgroup (Table 1), the analysis was repeated for various subsets: first, repeated, LRD, and CD transplants (Table 2). In all subsets, however, the results were consistent with those of the overall analysis, i.e., shorter patient survival in the diabetic subgroup and no significant difference in graft survival between the subgroups. Thus, the similar overall graft survival in the two subgroups cannot be attributed to bias due to differences in donor type or the number of transplants.

Moreover, multivariate analysis of data for transplants performed before or after 1988 showed no significant relationship between graft survival and the presence or absence of diabetes (Table 3). Retransplantation and the year of operation were significant determinants of outcome during the entire study period, as was donor type during the early period (1972–1987).

All of the above survival analyses were censored for patient death with a functioning graft, thus evaluating graft outcome during the patients' lifetime. The subgroup similarity in graft survival may also be considered in relation to the patient survival data. At the conclusion of the retrospective study (October 1995), the proportion of patients who had died with functioning grafts was higher in the diabetic than in the nondiabetic group (42 % vs 21 %; $P < 0.001$; Table 4). Accordingly, a smaller proportion of the original diabetic subgroup was still alive with functioning grafts, 38 % (72/189) as compared with the nondiabetic subgroup 54 % (324/599; $P < 0.001$). However, of the patients still alive, the proportion with functioning grafts was similar in the two subgroups [87 % (72/83) vs 82 % (324/393), respectively]. These figures are consistent with the results of

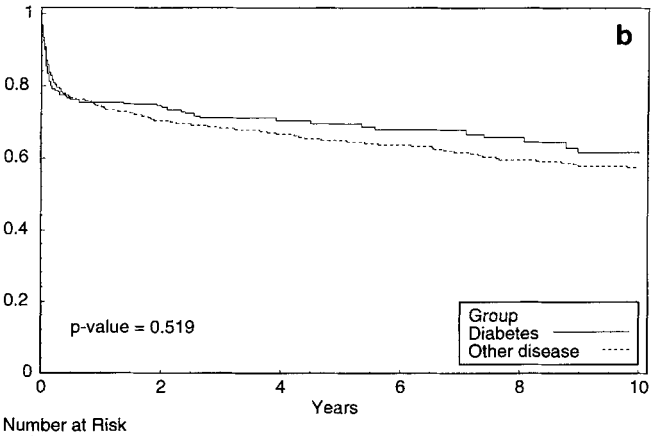
Patient survival



Number at Risk

185	140	106	86	65	49
586	501	392	324	238	176

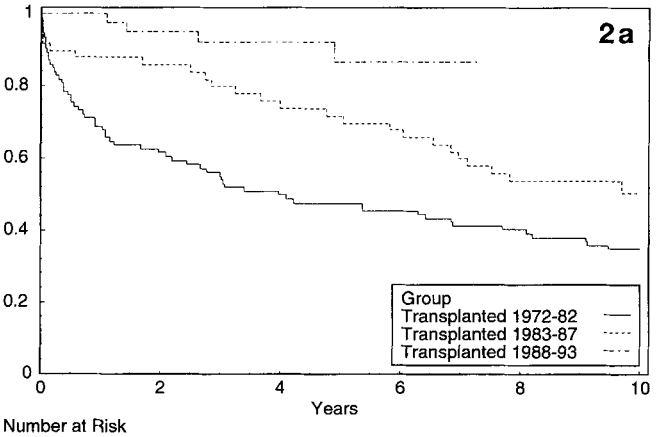
Graft survival



Number at Risk

223	137	101	75	55	36
734	459	334	256	174	118

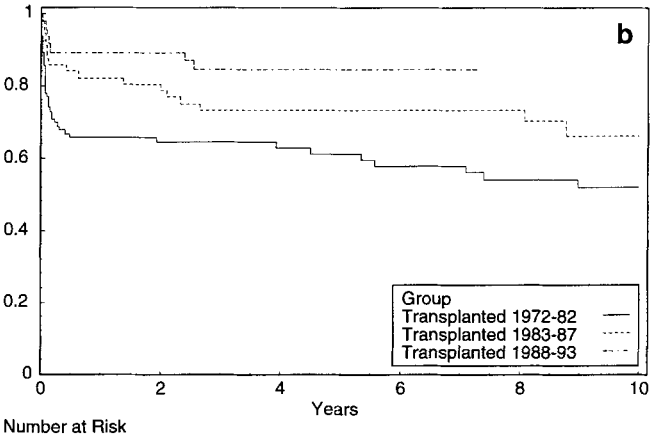
Patient survival



Number at Risk

94	58	47	43	38	33
50	43	38	34	27	16
41	39	21	9	0	0

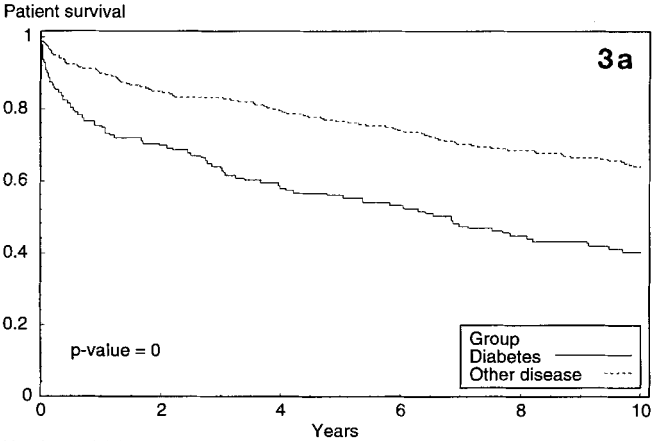
Graft survival



Number at Risk

115	50	41	34	29	23
60	45	37	32	26	13
48	42	23	9	0	0

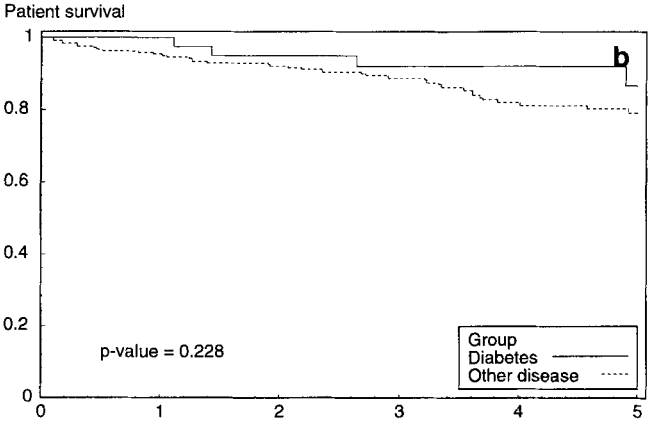
Patient survival



Number at Risk

144	101	85	77	65	49
363	309	290	270	238	176

Patient survival



Number at Risk

41	41	39	30	21	15
223	213	192	151	102	81

Table 3 Relationship between graft survival and several clinical variables in the two parts of the study period (Cox multivariate analysis)

Variable	Transplants 1972–1987		Transplants 1988–1993	
	Hazard ratio	*P* value	Hazard ratio	*P* value
Presence of diabetes	0.89	0.4	0.6	0.3
Cadaveric donor	2.0	< 0.001	1.2	0.5
Retransplantation	1.4	< 0.01	1.8	< 0.01
Year of transplantation	0.96	< 0.01	0.87	0.07
Male recipient	1.1	0.4	1.3	0.2
Recipient age	0.99	0.1	0.99	0.7

Table 4 Clinical outcome of diabetic and nondiabetic patients who received one or more renal allografts during the 22-year period, 1972–1993, evaluated at the end of the retrospective study (October 1995)

Outcome	Diabetics		Nondiabetics	
	n	[%]	*n*	[%]
Died with functioning graft	80	(42)	127	(21)**
Died after graft loss	21	(11)	73	(12)
Alive with functioning graft	72	(38)	324	(54)**
Alive with graft gloss	11	(6)	69	(12)*
Alive, all	83	(44)	393	(66)**
Total	189		599	
Proportion (%) functioning grafts in patients still alive	87		82	

* $P < 0.05$; ** $P < 0.001$

life-table analysis censored for patient death and show graft survival to be similar in diabetic and nondiabetic patients during the remainder of their lives after transplantation.

Overall treatment success was evaluated in terms of graft survival analyzed with failure defined as graft loss or patient death. In the early part of the study (1972–1987), treatment success was significantly inferior in the diabetic subgroup ($P < 0.05$). The rate of graft loss was similar in patients in the two subgroups, but mortality was higher among diabetic patients. In the latter part of the study (1988–1993), both mortality and graft loss rates were similar in the two subgroups and, consequently, the subgroups did not differ significantly in treatment success (proportion alive with functioning graft; $P = 0.3$).

Total mortality was 106 (56 %) in the diabetic subgroup and 206 (34 %) in the nondiabetic subgroup (Table 5). The most common cause of death was cardiovascular or cerebrovascular disease, which occurred in 46 % of cases in the diabetic subgroup and in 44 % in the nondiabetic subgroup. Life-table analysis with death due to cardiovascular or cerebrovascular disease as the terminal event showed that before 1988, patients in the diabetic subgroup died significantly more often from this cause than patients in the nondiabetic subgroup did ($P < 0.001$), but in the latter part of the study there was no difference ($P = 0.9$). From the life-table in Fig. 2a, it was demonstrated that the improved treatment success rate for the diabetic patients was based on a reduction in early post-transplant mortality. This prompted a final analysis of cause of death during the 1st postoperative year (Table 6). The improvement in patient survival in the diabetic subgroup was caused by a significant reduction in cardiovascular or cerebrovascular mortality ($P < 0.05$) and in deaths from other causes ($P < 0.001$). Taken together, the 1st year mortality rate in the diabetic subgroup decreased from 24 % in transplants before 1988 to 0 % in those performed thereafter.

◀ **Fig. 1** **a** Cumulative patient survival after first renal transplantation in 1972–1993 in diabetic ($n = 185$) and nondiabetic ($n = 586$) subgroups ($P < 0.001$). **b** Cumulative graft survival after renal transplantation in 1972–1993 in diabetic ($n = 223$)and nondiabetic ($n = 734$) subgroups ($P = 0.5$)

Fig. 2 **a** Cumulative patient survival after first renal transplantation among diabetic patients alone ($n = 185$) during three different periods: 1972–1982 ($n = 94$), 1983–1987 ($n = 50$), and 1988–1993 ($n = 41$). **b** Cumulative graft survival after renal transplantation among diabetic patients ($n = 223$), during the same periods: 1972–1982 ($n = 115$), 1983–1987 ($n = 60$), and 1988–1993 ($n = 48$)

Fig. 3 **a** Cumulative patient survival after first renal transplantation in 1972–1987 in diabetic ($n = 144$) and nondiabetic ($n = 363$) subgroups ($P < 0.001$). **b** Cumulative patient survival after first renal transplantation in 1988–1993 in diabetic ($n = 41$) and nondiabetic ($n = 223$) subgroups ($P = 0.2$)

Discussion

Among renal transplant recipients, life expectancy has generally been significantly shorter in diabetic patients than in nondiabetic patients. This study showed the success rate of renal transplantation performed after 1988, when a new protocol had been introduced, to be similar in diabetic and nondiabetic patients for up to 5 years post-transplantation. During the 22-year study period as a whole, patient survival increased in both subgroups, but most dramatically among patients with diabetic nephropathy. Graft survival during the remainder of the patient's life after transplantation was similar in the two subgroups throughout the 22-year period.

Table 5 Causes of death among diabetic (n = 189) and nondiabetic (n = 599) recipients of renal allografts during the 22-year period, 1972–1993. The mortality rate was 56 % among diabetic and 34 % among nondiabetic patients

Cause of death	Diabetics		Nondiabetics	
	n	[%]	n	[%]
Cardiovascular and cerebrovascular	49	(46)	90	(44)
Myocardial ischemia, infarction, or cardiac arrest	19	(18)	37	(18)
Cardiac failure	17	(16)	27	(13)
Cerebrovascular event	8	(8)	16	(8)
Pulmonary embolus	5	(5)	2	(1)
Other			8	(4)
Infection	7	(7)	25	(12)
Viral			6	(3)
Bacterial	6	(6)	19	(9)
Fungal	1	(1)		
Malignant disease	2	(2)	19	(9)
Other	41	(39)	62	(30)
Not known	7	(7)	10	(5)
Total mortality	106		206	

Table 6 Mortality rates in the 1st post-transplant year, grouped by cause of death, in diabetic and nondiabetic recipients of a first renal transplant, comparing the early (1972–1987) and the late (1988–1993) parts of the study

Years of transplant	Diabetic patients		Nondiabetic patients	
	Cerebrovascular or cardiovascular n/N [%]	Other cause of death n [%]	Cerebrovascular or cardiovascular n/N [%]	Other cause of death n [%]
1972–1987	16/144 (11)*	19 (13)**	15/363 (4)	20 (6)
1988–1993	0/41 (0)	0 (0)	4/223 (2)	6 (2)

* $P < 0.05$; ** $P < 0.01$

These improvements in treatment success rate for diabetic patients were shown to be associated with a reduced risk during the 1st postoperative year of death from cardiovascular or cerebrovascular events and of death from other causes. In accordance with findings by others [12–15], cardiovascular or cerebrovascular disease was found to be the most common cause of death throughout the study period. In this study, diabetic patients transplanted before 1988 were at significantly greater risk of cardiovascular and cerebrovascular death than were nondiabetic patients. We can now report that in diabetic patients transplanted since the end of the 1980s, the rate of cardiovascular and cerebrovascular deaths has decreased and there is no longer any significant difference in this respect between them and other renal transplant patients. These improvements in outcome, manifest not only after 1 year but also after 5 years, were probably due to improved initial and general management of diabetes mellitus instituted at least a decade ago.

This study was designed to evaluate long-term outcome, and a median follow-up of 8 years (with a minimum of 2 years) was achieved since those included were patients transplanted during the 22-year period from 1972 to 1993. Treatment results were evaluated with various methods. As a large proportion of renal transplant patients, both diabetics and others, may die of causes unrelated to transplantation, graft survival analyses in this study were censored for patient death with a functioning graft in order to focus on graft outcome during the rest of the patient's life. Patients who died with functioning grafts were statistically considered as lost to follow-up. Parallel analyses of graft and patient survival were, therefore, complementary for the evaluation of outcome, and both were combined in one actuarial analysis of treatment success, not censored for patient death, and in one analysis of the treatment success rate at the end of the study period (Table 4). Stratification for variables such as donor type and transplant number was done by means of multiple life-tables (Table 2) and a multivariate analysis. In the latter test, it was evident that graft outcome was independent of the presence or absence of diabetes but dependent on primary transplantation versus retransplantation and on the date of transplantation, that is, the improvement of results year by year. Additionally, in the early part of the study, cadaveric donor transplants carried an elevated risk of short graft survival.

Selection criteria for renal transplantation may affect the results. Patients referred for renal transplantation were reviewed by transplant nephrologists and transplant surgeons at this unit, all of whom were keen to keep selection criteria constant or perhaps manifested a tendency to increase the acceptance rate for the wait-

ing list. During the latter part of the study (1988–1993), greater efforts were made to exclude patients with cardiovascular disease, but the number of diabetic patients denied renal transplantation did not increase. At our unit, only one or two diabetic patients a year have been denied this treatment over the last 10 years, and a similarly small number of patients were treated before transplantation with percutaneous coronary angioplasty or a coronary bypass operative procedure. Much effort was made to ensure a thorough examination before transplantation to identify cardiovascular disease and other risk factors and to reduce them if possible [17]. Screening for cardiovascular disease has been suggested even for asymptomatic diabetic patients prior to acceptance for renal transplantation, due to the high prevalence of cardiovascular events [12]. However, there has been much debate as to whether myocardial scintigraphy is enough to identify all patients at risk of cardiovascular disease, or whether routine coronary angiography should be performed as well [10, 12, 17]. At our center, a thallium stress test is undergone by all diabetic renal transplant candidates and coronary angiography is performed in cases of reversible ischemia or clinical signs of coronary insufficiency. Possible beneficial effects of these measures were reflected in the results of this study.

Improved 1-year and 2-year survival rates among diabetic renal recipients have been reported by other groups during recent years [6, 22, 23]. The most striking results have been obtained among diabetic patients receiving grafts from living donors [22, 23]. Diabetic patient survival among cadaver kidney recipients also improved during the 1980s, but it has still been shorter than that of nondiabetic patients after more than 2 years' follow-up [9, 23, 25]. Several studies during the 1980s showed 5-year patient and graft survival rates to be significantly lower among diabetic than among nondiabetic recipients [12, 19]. In contrast, this study and two recently published studies [1, 21] have demonstrated 5-year graft and patient survival rates to be similar among diabetic and nondiabetic patients transplanted in the late 1980s and early 1990s.

A large part of the dramatic improvement in patient survival during the 1980s, as compared to the previous decade, may be attributed to a reduced risk of early post-transplant death, better 1st year graft survival, and a reduction in the number of patients who die with functioning grafts [8]. These were benefits enjoyed by all patient categories and may be explained by alterations in immuno-suppressive drug and maintenance protocols (the introduction of CyA), in diagnostic procedures and treatment of rejection (biopsy techniques, OKT3, ATG, and immunoadsorption), and in the treatment and prevention of infectious diseases. The overall gain in graft survival rates in the 1980s has been postulated to be due to fewer cases of acute rejection and fewer deaths due to infection [20]. The improvement in treatment success rates among diabetic patients may also be ascribable to the abovementioned factors, as well as to specific changes in diabetes care, including multiple insulin dose regimens and treatment for cardiovascular disease, edema, and hypertension during the last 10 years, resulting in less angiopathy and, thus, better patient survival [2, 5].

Late complications related to diabetes mellitus and multiple organ involvement, primarily cardiovascular disease, continue to progress despite successful renal transplantation [7]. It remains to be seen what the patient survival rates may be after more than 10 years with modern transplantation monitoring; one cannot rule out the possibility that they might be less favorable among patients with diabetic nephropathy than among other renal transplant recipients. However, the results of this study clearly demonstrate that diabetic patients who develop uremia are not as high risk patients as they once were, and that renal transplantation is a safe and effective treatment modality for them as well as for patients with other forms of renal disease.

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