Combined Pancreas-Kidney Transplantation for Patients With End-Stage Nephropathy Caused by Type-2 Diabetes Mellitus

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Background. Simultaneous pancreas-kidney (SPK) transplantation is widely accepted as an optimal therapeutic option for patients with type 1 diabetes mellitus (T1DM) and end-stage renal disease, but the indication for patients with type 2 diabetes mellitus (T2DM) is still controversially discussed.

Methods. Twenty-one T2DM recipients of a first combined pancreas-kidney graft performed at our center during a 9-year period were retrospectively analyzed with regard to demographic characteristics; cardiovascular risk factors; surgical, immunological, and infectious complications; and patient and graft survivals and compared with T1DM recipients (n=195) and 32 T2DM patients who received a kidney transplant alone (KTA) during the same period.

Results. Patient survival at 1 and 5 years was 96.9% and 91.6% for the T1DM group, 90.5% and 80.1% for the T2DM group, and 87.1% and 54.2% for the T2DM KTA group, respectively ($P<0.001$). Actuarial pancreas graft survival for SPK recipients at 1 and 5 years was calculated to be 92.6% and 80.7% for the T1DM group and 81.0% and 75.9% for the T2DM group, respectively ($P=0.19$). Kidney allograft survival at 5 years was 83.6% for T1DM, 80.4% for T2DM, and 52.7% for T2DM KTA ($P<0.0001$). Multivariate analysis adjusting for donor and recipient age, secondary complications of diabetes, body mass index, waiting time, cold ischemic time, delayed graft function, and coronary risk factors showed that differences did not remain statistically significant.

Conclusion. Favorable results can be achieved with SPK transplantation in type 2 diabetics with a low coronary risk profile. A high cardiac death rate impacts results of KTA and calls for stringent selection.

Keywords: Simultaneous pancreas-kidney transplantation, Type 2 diabetes mellitus.

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Since the first pancreas transplantation was performed in 1966, it has evolved into the gold standard for endocrine replacement of β-cells in patients with type 1 diabetes mellitus (T1DM) and end-stage renal disease (ESRD). Nevertheless, its usefulness in the management of type 2 diabetes mellitus (T2DM) is not unanimously acknowledged (*1*, *2*). When performed as simultaneous pancreas-kidney (SPK) transplantation, it has been shown to render also T2DM patients independent of insulin and renal replacement therapy. Type 2 makes up for more than 95% of all diabetics and has become the leading cause of ESRD. Changes in lifestyle particularly concerning quality and quantity of nutrition resulting in increased body weight have to be considered as main causes of this evolution. According to the International Pancreas Transplant Registry (IPTR), up to 10% of SPK transplant recipients have been classified as T2DM. Differentiation between T1DM, T2DM, and other types of DM may sometimes be difficult. Whereas clinical and epidemiologic characteristics of DM have an impact on the outcome of SPK transplantation, it seems not to be affected by C-peptide status (*3*). It is shown that peripheral insulin resistance and consecutive β-cell overstimulation and exhaustion do not occur after pancreas transplantation because no recurrences of T2DM have been observed. Several single-center retrospective studies report outcomes equivalent to those for pancreas transplantations in T1DM recipients (*2*). In this study, we retrospectively analyzed 21 T2DM SPK recipients with regard to postoperative complications and long-term outcome after SPK and compared the results with those of SPK recipients with T1DM and of T2DM recipients of a kidney transplant alone (KTA).

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TABLE 1. Quantitative and qualitative patient characteristics at baseline according to study group

A. Quantitative patient characteristics

	T1DM SPK (n=195)		T2DM SPK (n=21)		T2DM KTA (n=32)		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	***P***
Recipient age, y	41.6	9.2	53.6	5.9	63.5	5.6	<0.001
PRA, %	2.4	9.1	3.6	11.0	0.5	2.3	0.424
Donor age, y	31.3	10.8	34.2	11.7	52.4	17.0	<0.001
CIT, hr	13.1	3.1	13.6	3.5	15.8	4.1	<0.001
Waiting time, mo	6.2	7.1	7.6	9.1	24.6	20.5	<0.001
BMI, kg/m^2	23.4	3.1	25.1	3.3	26.6	2.5	<0.001
Cholesterol, mg/dL	195	45	188	50	193	55	0.786
Triglycerides, mg/dL	147	78	144	69	173	96	0.221
HDL, mg/dL	59	20	51	14	53	19	0.067
LDL, mg/dL	106	38	102	47	113	48	0.608
Systolic blood pressure, mm Hg	131	11	138	24	138	12	0.014
Diastolic blood pressure, mm Hg	77	7	82	9	78	8	<0.001
HbA1c pretransplantation, %	7.5	1.2	8.6	1.5	—	—	0.067
Age at onset, y	[17.6]	12.5	37.8	6.7	48.4	9.0	0.006

B. Qualitative patient characteristics	**T1DM SPK, n (%)**	**T2DM SPK, n (%)**	**T2DM KTA, n (%)**	***P***
Gender				
Male	130 (66.6)	17 (80.9)	29 (90.6)	<0.012
Female	65 (33.4)	4 (19.1)	3 (9.4)	
Arterial obstructive disease				
Yes	46 (23.6)	16 (76.2)	19 (59.4)	<0.001
No	149 (76.4)	5 (23.8)	13 (40.6)	
Retinopathy				
Yes	26 (13.4)	16 (76.1)	16 (50.0)	<0.001
No	169 (86.6)	5 (23.9)	16 (50.0)	
Neuropathy				
Yes	15 (7.7)	15 (71.4)	5 (15.6)	<0.001
No	180 (92.39)	6 (38.6)	27 (84.4)	
Nephropathy				
Yes	195 (100)	21 (100)	32 (100)	NA
No	0 (0)	0 (0)	0 (0)	
Number of antihypertensive drugs				
0	66 (33.9)	0 (0)	0 (0)	<0.001
1	75 (38.5)	5 (23.8)	5 (15.6)	
2	41 (21.0)	5 (23.8)	17 (53.1)	
3	12 (6.1)	8 (38.1)	8 (25.0)	
4	1 (0.5)	3 (14.3)	2 (6.3)	
Coronary heart disease				
Yes	59 (30.3)	12 (57.1)	26 (81.2)	<0.001
No	136 (69.7)	9 (42.9)	6 (18.8)	
CABG/stent				
Yes	6 (3.1)	2 (9.5)	18 (56.2)	<0.001
No	189 (96.9)	19 (90.5)	14 (43.8)	

BMI, body mass index; CABG, coronary artery bypass graft; CIT, cold ischemic time; HDL, high-density lipoprotein; KTA, kidney transplant alone; LDL, low-density lipoprotein; NA, not applicable; PRA, panel reactive antibodies; SPK, simultaneous pancreas-kidney; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

RESULTS

The study population included 216 patients receiving a first SPK transplant between February 2000 and September 2009, 21 of whom were classified as having T2DM according to the study criteria and 32 T2DM recipients of a kidney alone during the same period. All of the T2DM recipients of SPK and 30 of 32 T2DM recipients were on exogenous insulin and had a history of oral antidiabetic medication for at least 6 months. Two of the latter group were oral antidiabetics at the time of transplantation. Patient characteristics and various baseline data such as recipient and donor age, body mass index (BMI), lipid metabolism, blood pressure, HbA1c, age at onset of disease, preformed human leukocyte antigen (HLA) antibodies, and time on the waiting list are summarized in Table 1A. A significant difference between the three groups was identified with regard to recipient and donor age, age at disease onset, cold ischemia time, BMI, diastolic blood pressure, and waiting time. Table 1B depicts further characteristics including gender, secondary complications of diabetes, antihypertensive medication, arterial obstructive and coronary heart disease, and coronary interventions. A statistically significant difference was detected for all of these characteristics between the three groups.

The number of surgical and infectious complications, incidence of rejection and delayed graft function, and C-peptide and serum creatinine levels at discharge are shown in Table 2. The difference in delayed kidney graft function in the T2DM KTA group turned out to be significant ($P<0.001$), and the number of steroid-free immunosuppression after 12 months was higher in the SPK groups ($P<0.0001$).

Patient survival at 1, 3, and 5 years was significantly higher in type 1 diabetics as compared with the two type 2 groups (Fig. 1 and Table 3). Pancreas graft survival censored and not censored for death was better at all three time points in the T1DM SPK group but did not reach statistical significance. Mean (SD) follow-up was 7.3 (3.0) years. Survival differences between groups adjusting for donor and recipient age, secondary complications of diabetes, BMI, waiting time, cold ischemic time, delayed graft function and coronary risk factors were no longer statistical significant in multivariate analysis. Table 4 summarizes the causes of death and graft loss.

DISCUSSION

Of the overall U.S. population, 7.8% suffer from DM, whereas the prevalence in Germany and Northern Europe is only slightly lower (7.6%) (*4*). T2DM accounts for up to 95%, and T1DM, for approximately 5%, of all cases of DM (*2*, *5*). With the increasing epidemic of T2DM, the prevalence of ESRD caused by DM has risen from 15% in 1980 to 45% in 2000 and is expected to rise further (*6*). According to the IPTR, up to 10% of all SPK transplantations were performed in patients with T2DM and ESRD (*7*). Differentiation between T1DM and T2DM corresponding to the presumed mechanisms may be difficult because the two groups clinically overlap. According to the "accelerator hypothesis" formulated by T. J. Wilkin, T1DM and T2DM are believed to be the same disorder of insulin resistance set against different backgrounds and determined by the impact of environmental and behavioral variables accompanied by different genetic backgrounds (*2*, *8*). In addition to that, special entities extend the spectrum of the disease. Maturity onset diabetes in the young (types 1–6) has autosomally determined deficiencies in β-cell function, which may lead to insulin dependence without autoimmunity

TABLE 2. Clinical data of the study groups

	T1DM SPK, n (%)	T2DM SPK, n (%)	T2DM KTA, n (%)	*P*
Surgical complications				
Male	38 (19.5)	7 (33.3)	8 (25)	0.294
Female	157 (80.5)	14 (66.7)	24 (75)	
Acute rejection				
Yes	18 (9.3)	2 (10.0)	3 (9.4)	0.994
No	177 (90.7)	18 (80.0)	29 (90.6)	
Infectious complications				
Yes	32 (16.3)	4 (19.0)	9 (28.9)	0.272
No	164 (83.7)	17 (81.0)	23 (71.9)	
DGF pancreas				
Yes	32 (16.4)	3 (15.0)	NA	0.872
No	163 (83.5)	17 (85.0)		
DGF kidney				
Yes	24 (12.3)	3 (15.0)	19 (59.4)	<0.001
No	171 (87.7)	18 (85.7)	13 (40.6)	
Steroid-free after 12 months				
Yes	150 (76.9)	13 (61.9)	12 (37.5)	<0.0001
No	45 (23.1)	8 (38.1)	20 (62.5)	
C-peptide at discharge, mean (SD), ng/mL	5.6 (3.5)	4.2 (2.1)	—	0.131
Creatinine at discharge, mean (SD), mg/dL	1.0 (0.4)	1.1 (0.3)	1.9 (1.3)	0.021

DGF, delayed graft function; KTA, kidney transplant alone; NA, not applicable; SPK, simultaneous pancreas-kidney; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

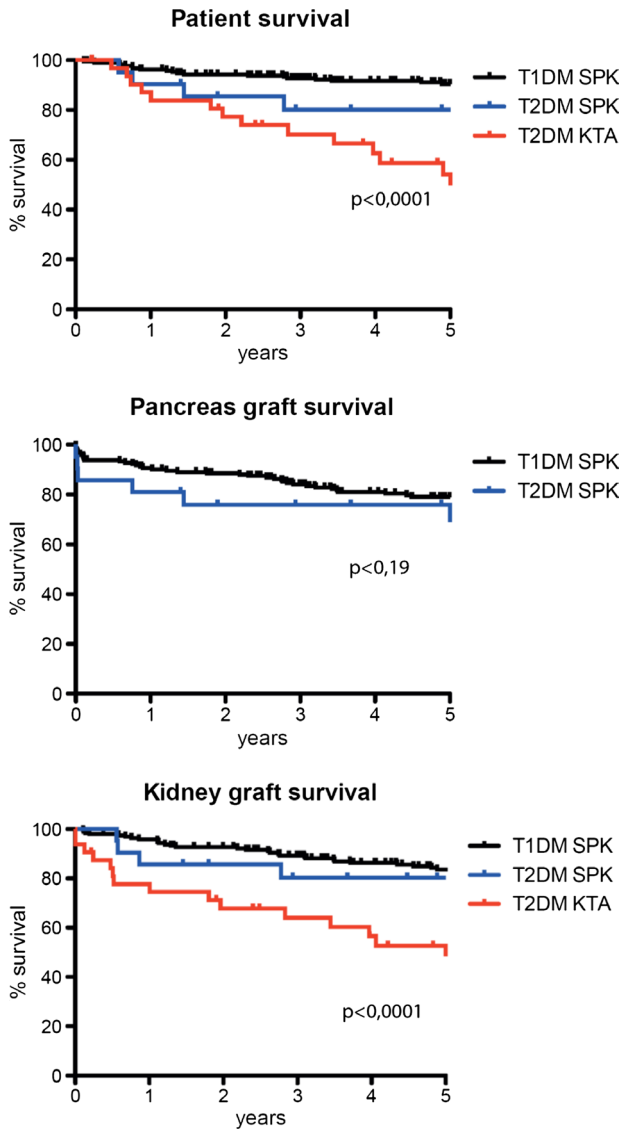

FIGURE 1. Patient survival and pancreas and kidney graft survivals in the T1DM SPK, T2DM SPK, and T2DM KTA groups.

in younger individuals (*2*). On the other hand, patients with late autoimmune DM in adults have usually developed antibodies against glutamic acid decarboxylase that cause insulin deficiency soon after appearance in older patients (*5*, *9*).

So far, no reliable and objective tests exist for the differentiation between T1DM and T2DM. Many authors and diabetic societies have defined discriminating criteria such as age at diagnosis, BMI, family history, HLA association, detectable C-peptide, and antibodies. However, several patients do not fit into one category only. For most authors (*2*), fasting or stimulated C-peptide levels have, for a long time, been the main criterion for defining T2DM (*2*, *10*). However, this point must be seen critically: As the kidney is the major site of C-peptide metabolism, C-peptide levels in patients with renal disease can be high but not representative (*5*) and therefore do not reflect the actual functioning β-cell mass (*2*, *6*, *7*). Furthermore, with ultrasensitive methods, C-peptide has been detected in 10% of T1DM patients up to 30 years after the onset of diabetes (*11*).

The typical T2DM patient is older and obese and shows the aspect of metabolic syndrome (*2*). The difference in BMI between type 1 and type 2 diabetics in our study is statistically significant in univariate analysis only and is clinically irrelevant. In T2DM patients, peripheral insulin resistance, which is associated with relative insulin deficiency and insulin secretory defect, plays a central role. The hypothesis that transplanted β-cells in those patients are overstimulated, which again would lead to β-cell exhaustion and graft failure, was not confirmed by others (*3*). Apart from that, the pretransplantation C-peptide status did not influence the outcome of SPK transplantations in T2DM patients (*12*). In another study, the effect on insulin secretion and sensitivity in a T2DM SPK transplant recipient was carefully examined. The patient was insulin resistant before surgery, and insulin sensitivity declined further after transplantation, which was probably caused by immunosuppressive medication including glucocorticoids, but improved in the longer term. Insulin secretion was greatly impaired before and early after surgery, presumably because of steroids and organ damage, but also improved in the long term (*13*).

Patient survival, however, in univariate analysis only, was seen to be significantly inferior in the T2DM group. We were not able to confirm significant survival differences in the multivariate analysis. The small sample size in T2DM patients and the effects of confounding variables, especially recipient age, were the reasons for not achieving statistical significance. Similar results have also been reported by Singh et al. (*14*) in a small series of patients. Unfortunately, in our cohort, the survival rate was impacted by late fatal fungal infection in two recipients. No increase in immunosuppression preceded these two lethal infections. Pancreas graft survival in T2DM was less favorable than in the T1DM group but did not reach statistical significance. The surgical complication rate requiring reoperation in our T2DM SPK group was found not to be higher than in other series of pancreas transplantation in T1DM (*15*, *16*). Alarmingly high was the complication rate in the T2DM KTA recipients group (Table 2).

Patient survival and renal allograft survival were worst in the KTA group. However, these patients were older and showed a higher incidence of coronary heart disease and secondary complications of diabetes (Table 1A,B).

Poor kidney graft survival in this group was mainly caused by primary nonfunction in three patients and the death of nine patients with a functioning graft. The reason for the unusually high initial nonfunction rate in KTA recipients remains unclear because cold ischemia time was similar to that of the other two groups, and although significantly higher than in pancreas recipients, donor age was not particularly high. The poor quality of donor organs in the KTA group is also reflected by the higher serum creatinine level. Waiting time was significantly longer in the KTA group and caused by current Eurotransplant allocation rules. These favor combined pancreas-kidney recipients, which could be a reason to aim for as many SPK transplantations as possible. However, none of our T2DM KTA recipients would have qualified for a combined transplantation. Apart from that, it has been shown that patients after a combined transplantation showed a substantially improved survival when compared with diabetic recipients of a kidney alone (*17*).

TABLE 3. Summary of patient and graft survival rates

	T1DM SPK, %		T2DM SPK, %		T2DM KTA, %		*P*	
Patient survival								
1-y	96.9		90.5		87.1		<0.001	
3-y	94.2		80.1		70.2			
5-y	91.6		80.1		54.2			
Pancreas graft survival								
	NCFD	DC	NCFD	DC	NCFD	DC	NCFD	DC
1-y	92.6	93.2	81.0	85.7			0.19	0.35
3-y	85.8	89.1	75.9	85.7	NA			
5-y	80.7	85.0	75.9	85.7				
Kidney graft survival								
	NCFD	DC	NCFD	DC	NCFD	DC	NCFD	DC
1-y	95.9	98.4	85.7	90.2	77.7	80.6	<0.0001	0.09
3-y	89.3	94.5	80.4	90.2	64.0	80.6		
5-y	83.6	89.8	80.4	90.2	52.7	80.6		

DC, death-censored; KTA, kidney transplant alone; NA, not applicable; NCFD, not censored for death; SPK, simultaneous pancreas-kidney; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Although type 2 accounts for more than 95% of patients with diabetes, only few pancreas transplantations reported to the IPTR have been performed in type 2 diabetics (*15*). The reluctance of some groups to perform SPK in patients with T2DM is most likely because of the fact that the mechanism by which a pancreas allograft overcomes insulin resistance is not fully understood. Furthermore, a high cardiovascular risk, obesity, and advanced secondary complications of diabetes often associated with T2DM may deter some surgeons from accepting these patients for transplantation.

Changes in lifestyle and diet may help reduce the incidence of T2DM (*18*). Morbidly obese patients may derive benefit from bariatric surgery with regard to the potentially reverse effects of type 2 diabetes (*19*). Whether T2DM can be

TABLE 4. Causes of death and causes of graft loss

	T1DM SPK, n (%)	T2DM SPK, n (%)	T2DM KTA, n (%)
Cause of death			
MI	9 (4.6)	1 (0.5)	8 (25)
Malignancy	4 (2.0)	1 (0.5)	1 (3.1)
Pulmonary infection	4 (2.0)	2 (9.5)	4 (12.5)
Sepsis	4 (2.0)	1 (0.5)	1 (3.1)
Stroke	2 (1)	1 (0.5)	—
Hemorrhage	1 (0.5)	—	—
Cause of pancreas graft loss			
Patient death	18 (9.3)	3 (14.3)	NA
Rejection	35 (17.8)	1 (4.7)	
Thrombosis	9 (4.6)	2 (9.5)	
Graft infection	3 (1.5)	1 (4.7)	
Bleeding	1 (0.5)	—	
Pancreatitis	—	1 (4.7)	
Cause of kidney graft loss			
Patient death	17 (8.8)	4 (19)	9 (27.3)
Rejection	19 (9.7)	3 (14.3)	3 (9.3)
Thrombosis	3 (1.5)	—	—
Infection	1 (0.5)	1 (4.7)	1 (3.1)
Recurrence of GN	1 (0.5)	—	—
Hemorrhage	1 (0.5)	—	—
Primary nonfunction	—	—	3 (9.3)

GN, glomerulonephritis; KTA, kidney transplant alone; MI, myocardial infarction; NA, not applicable; SPK, simultaneous pancreas-kidney; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

cured by islet transplantation remains to be seen (*20*). Other treatment options for insulin-dependent diabetes would be insulin pumps, which are still not able to control diabetes in a fully automated fashion, or closed-loop systems with integrated glucose sensors (*21*).

Our study is among the few reports of successful pancreas transplantation in T2DM patients in Europe. A few series have been reported from Spain (*11*) and Italy (*22*), and five cases were reported from Germany (*23*), where most centers still consider T2DM to be a contraindication for pancreas transplantation. Available data suggest, however, that T2DM patients not be excluded from combined pancreas-kidney transplantation as a matter of principle.

The limitation of this report is certainly its retrospective nature of data acquisition and the limited number of patients in the T2DM group. Prospective randomized trials comparing SPK, KTA, and intensified insulin treatment are highly warranted. According to the selection criteria proposed by other groups (*24*), we conclude from our experience that select type 2 diabetics with an acceptable coronary risk profile and not more than 55 years can benefit from a combined kidney-pancreas transplantation.

MATERIALS AND METHODS

Patients

After approval by the local ethics committee, data from all patients transplanted between February 2000 and September 2009 were retrospectively analyzed. Patient and graft survivals after SPK transplantation were compared between the T1DM and the T2DM groups. Thirty-two type 2 diabetic recipients of a kidney alone served as another control group. Patients with a low cardiovascular risk profile (no history of angina pectoris or smoking; no wall motion abnormalities on echocardiogram; ejection fraction, >50%; no previous limb amputation; and BMI, <32) were considered suitable for a combined transplantation. Indication for KTA was mainly based on age and general condition.

Fasting C-peptide was used as the main criterion for defining T2DM, and the absence of autoantibodies (against islet cells, insulin, glutamic acid decarboxylase, or tyrosine phosphatase IA2) (*25*). T1DM was defined as an early-onset disease with a sudden need for insulin, presence of one or more autoantibodies, and C-peptide negativity. Patients with a BMI higher than 32 kg/m^2 and a positive crossmatch against donor cells were excluded. The following pretransplantation data were collected: recipient and donor age, BMI, lipid metabolism, blood pressure, HbA1c levels, age at the onset of diabetes, preformed HLA antibodies, and time on the waiting list. Pretransplantation qualitative data included gender, secondary complications of DM (nephropathy, neuropathy, and retinopathy), arterial obstructive disease, coronary heart disease, coronary revascularization, and number of antihypertensive drugs. Clinical data composed of surgical and infectious complication rate, number of acute rejections, delayed graft function of the pancreas and kidney graft, C-peptide and serum creatinine at discharge, and the number of patients with steroid-free immunosuppression after 12 months.

Surgical Technique

The pancreas grafts were procured in a "no touch" technique en bloc with the spleen and the duodenum. University of Washington or histidine-tryptophan-ketoglurate solutions were used for in situ perfusion. Back-table preparation included removal of the spleen and the peripancreatic fat and arterial reconstruction using a donor iliac Y-graft. Pancreatic grafts were revascularized to the right common iliac artery in an end-to-side fashion and venously drained to the distal caval vein or the superior mesenteric vein. Exocrine drainage was achieved as a stapled or hand-sewn side-to-side duodenojejunostomy 25 to 50 cm beyond the flexure of Treitz.

Immunosuppression and Perioperative Antimicrobial Prophylaxis

Standard induction therapy consisted of 4 mg/kg body weight antithymocyte globulin, given as a single bolus. Tacrolimus was given to achieve whole-blood trough levels of 10 to 12 ng/mL for the first 3 months, 8 to 10 ng/mL for months 4 to 12, and 6 to 8 ng/mL thereafter. Mycophenolate mofetil was given at an oral dose of 1 g twice daily. A rapid steroid-tapering regimen was applied starting with 500 mg methylprednisolone administered intraoperatively to reach a dose of 25 mg prednisolone at the end of the first week after operation and further reduction to a daily maintenance dose of 5 mg. Whenever possible (stable graft function, no or only one rejection episode), steroids were discontinued at the end of the first year. For perioperative systemic antimicrobial prophylaxis, patients received piperacillin/tazobactam at a dose of 4.5 g and ciprofloxacin at a dose of 200 mg twice daily for 3 days, and fluconazole, 400 mg once daily for 7 days. Acute rejection of the pancreas was clinically determined by means of an increased serum amylase and lipase, a need for exogenous insulin, a low C-peptide, an impaired renal function and/or abdominal pain and fever, and confirmed by renal histology or, whenever possible, by enteroscopic graft duodenal biopsy. Clinically suspected rejection of the kidney was confirmed by histology in all cases. Rejection episodes were treated three times with 500 mg of methylprednisolone; steroid-resistant rejections, with antithymocyte preparations. Delayed endocrine graft function was defined as a need for exogenous insulin to keep blood glucose levels below 150 mg/dL 10 days after operation because, beyond that time, patients were expected to be on regular care status and diet. Delayed kidney function was defined as the need for dialysis within the first week after transplantation.

Data Collection and Statistical Analysis

Baseline data were retrospectively collected including preoperative patient data, perioperative and postoperative complications, graft loss, and death. Statistical analysis was performed using SPSS for Windows 20.0 (SPSS Inc., Chicago, IL) and GraphPad Prism 5 for OSX 10.6 (GraphPad Software Inc., La Jolla, CA). Baseline characteristics were compared with appropriate statistical significance testing including a chi-square test, analysis of variance, and a nonparametric Kruskal-Wallis test. Survival rates were calculated using the Kaplan-Meier method and compared with a log-rank test; multivariate analysis was performed with a Cox proportional hazards regression analysis. Data are reported as median with minimum/maximum range, mean (SD), or 25% or 75% quartile values. $P<0.05$ was considered statistically significant.

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