Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Progression of macrovascular diseases is reduced in type 1 diabetic patients after more than 5 years successful combined pancreas-kidney transplantation in comparison to kidney transplantation alone

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Keywords
macroangiopathy, pancreas-kidney transplantation, type 1 diabetes.

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Received: 23 March 2005
Revision requested: 22 April 2005
Accepted: 1 June 2005

doi:10.1111/j.1432-2277.2005.00182.x

Summary

Recent reports have demonstrated an improved cardiovascular outcome after simultaneous pancreas-kidney transplantation (SPKT) compared with kidney transplantation alone (KTA) in type 1 diabetic patients with end-stage renal disease. The purpose of this study was to determine the impact of SKPT and KTA on the progression of cerebrovascular disease (CVD), coronary heart disease (CHD) and peripheral vascular disease (PVD) 5 and 10 years after transplantation. Only patients with graft survival more than 5 years, were included in this study. In summary, 12 type 1 diabetic patients with SPKT and 10 diabetic subjects with KTA were evaluated. The immunosuppressive therapy was similar in both patient groups. The mean observation period was 124 (72–184) months in the SPKT group and 122 (64–216) months in the group with KTA. To investigate the vascular risk profile we examined mean HbA1c, blood pressure and lipid levels in both patient groups during the first 5 years (period I) and the second 5 years (period II) after transplantation (measurements at least at 3-month intervals). Additionally, we evaluated the prevalence of moderate (stage I–II) and severe (stage III–IV) macrovascular diseases prior as well as 5 and 10 years after transplantation. During period I the mean HbA1c-value was 5.7 ± 0.4% in the group with SPKT versus 7.4 ± 0.8% in the KTA group, and in period II 5.8 ± 0.4% in the SPKT group versus 7.6 ± 0.9% ($P < 0.001$) in the patients with KTA. The cholesterol levels were approximately the same in both groups, the triglycerides were lower in the patients with SPKT than in the subjects with KTA with 1.3 ± 0.4 vs. 2.2 ± 0.9 mmol/l in period I, and 1.4 ± 0.5 vs. 2.3 ± 0.6 mmol/l in period II ($P < 0.05$). The BP-values were similar in both groups. Five years after transplantation the prevalence of vascular diseases was not significantly different between both groups. During the following 5 years the prevalence of macrovascular diseases increased more in the KTA than in the SKPT group. After a mean observation period of 10 years the SKPT group showed a lower prevalence of vascular diseases (stage I–IV) with 41% CVD, 50% CHD and 50% PAV in comparison to the KTA group with a prevalence of 80% CVD, 90% CHD and 80% PAV), the difference was not statistically significant because of the small patient groups. The frequency of the vascular complications myocardial infarction (16% vs. 50%), stroke (16% vs.

40%) and amputations (16% vs. 30%) was in summary significant lower in the patients with SPKT than in the patients with KTA ($P < 0.05$). In conclusion, while for the first 5 years after transplantation the progression of macroangiopathy in patients with SPKT and KTA was not significantly different, after a mean 10-year observation period the progression of macrovascular diseases was significantly lower in recipients with a functioning SPKT compared to patients with a KTA; this can be explained by a better vascular risk profile after SPKT. The 10-year patient survival was 83% in the SPKT group and 70% in patients with KTA.

Introduction

During the last decade graft and patient survival steadily improved in type 1 diabetic patients after simultaneous pancreas-kidney transplantation (SPKT) [1–3]. In an earlier study the 1-year pancreas graft survival has been reported to be 81% for SPKT in a large data base [4], and the adjusted 10-year kidney graft survival 67% vs. 65% [5] for living donor kidney only and 46% for cadaver kidney transplant alone (KTA). In a recent study the one and 5-year pancreas graft survivals were 85% and 75% independent of HLA-matching. In the same study has been demonstrated that in patients with SPKT the pancreas transplants does not need to be allocated based on HLA matching criteria [6]. In the literature it was reported that long-term normoglycemia following pancreas transplantation can reverse diabetic retinopathy [7]. In a 10 year observation period of eight nonuremic type 1 diabetic patients it has been shown that pancreas transplantation is capable to reversing lesions of diabetic glomerulosclerosis. However, this reversion required more than 5 years of normoglycemia to be detectable and the major change in renal structure, i.e. the accumulation of extracellular matrix, however was found diminished only 10 years after successful pancreas transplantation, but not already after 5 years of graft survival [8]. In contrast to the reversal of microangiopathic lesions, first data in the literature about the impact of pancreas transplantation on the progression of macrovascular diseases were far from clear [9]. In one study the pancreas-kidney recipients had a significant higher incidence of peripheral vascular complications than those patients who received only a kidney graft [10]. In several recent studies reversal of macroangiopathic lesions with improved cardiovascular outcome has been reported. Positive effects were already demonstrable in short-term studies [11–13].

In our study we compared the progression of vascular diseases in type 1 diabetic patients with KTA and SPKT over a mean period of 10 years. In an earlier study with patients with at least 2-year functioning grafts there was no significant difference between the prevalence of vascular diseases 5 years after SPKN and KTA [14]. Hence, it was concluded that SPKT reduces cardiovascular risk factors but does not halt progression of macrovascular diseases during the first 5 years after transplantation.

The aim of this follow-up study was to determine the impact of SPKT and KTA on the progression of cerebrovascular disease (CVD), coronary heart disease (CHD) and peripheral vascular disease (PVD) during a mean observational period of 10 years after transplantation. Additionally, the vascular risk factors after SPKT and KAT were evaluated.

Patients and methods

Patients

Between 1990 and 1999 type 1 diabetic patients with graft survival after SPKT or KTA fore more than 5 years were recruited for this study. No KTA patient received a graft from a related donor. Diagnosis of type 1 diabetes was established by onset before age of 35 years and insulin requirement within 1 year after diabetes manifestation. C-peptide levels (measured in 21 patients) were <0.3 ng/ml before transplantation. Twelve type 1 diabetic patients with SPKT (age 35 ± 5 year) and 10 type 1 diabetic patients with KTA (age 43 ± 9 year) whose grafts functioned for at least 5 years were investigated in this retrospective study. The mean observation period was 124 (72–184) months in the SPKT group and 122 (64–216) months in the KAT group. All patients were routinely followed up at our outpatient care unit. In a retrospective analysis progression of vascular diseases was compared in patients with SPKT and with KTA during the first 5-year period after transplantation (period I: 64 ± 41 months) and additionally during the next 5-year period and beyond (period II: 62 ± 35 months). Risk factors for atherosclerosis (hyperglycemia, hypertension, hyperlipidemia, smoking) were investigated in both patient groups. The immunosuppressive therapy was almost identical in patients and included cyclosporine azathioprine and prednisolone. During the initial phase (4–12 weeks) after transplantation the cyclosporine doses were adjusted to maintain whole blood through levels of 150–200 ng/ml in patients with SPKT and 100–150 ng/ml in patients with KTA. Two patients with SPKT and one patient with KTA received mycophenolat mofetil and

tacrolimus. The blood levels of tacrolimus were kept at 12–16 ng/ml during the first 4–6 weeks after transplantation. Later on, lower blood levels were accepted (approximately 30% lower). Patients who received only kidney grafts were operated at the First Department of Surgery in the General Hospital Linz and patients with SPKT were operated at the Department of Transplant Surgery of the University of Innsbruck. In 10 patients segmental pancreas transplantation with systemic drainage and exocrine diversion to the bladder was performed as this was the standard procedure at that time. Two patients received a portal drainage of the pancreas graft. The KTA instead of SPKT was chosen in patients over 45 years of age ($n = 3$) which was at that time the age limit for pancreas transplantation, or when CHD ($n = 2$) was present. Other patients ($n = 5$) explicitly asked for KTA because they were afraid of the higher operative severity in SPKT. Patient- and graft survival were calculated for both groups after at 10 years of transplantation. Renal grafts were considered functioning as long as the patient did not require dialysis (GFR > 20 ml/min/1.73 m^2), and pancreas graft survival was considered when as long the patients did not require substitution of insulin. The baseline data of the patients (prior to transplantation) are summarized in Table 1.

Measurements

Following examinations were performed before and 5 years after transplantation as well as at the end of the observation period: 12-lead electrocardiogram and a Doppler blood flow study of the carotid arteries and of the peripheral arteries of the lower legs by using linear ultrasound Scanners (7.4 MHz Ultramark 5 and 9; Advanced Technology Laboratories, Vienna, Austria) including a physical examination. Additionally, a thallium scan was performed in all cases prior to transplantation, and a coronary angiography was performed in all patients above 40 years of age or in the patients with abnormal ECG or thallium scan. After the 5 year period with functioning grafts and at the end of the study the prevalence of all vascular diseases were evaluated. Also the frequency of interventions and of vascular complications such as stroke, myocardial infarction and amputation in history was recorded.

Moreover, the mean values of serum creatinine, hemoglobin, HbA1c, cholesterol, triglycerides (multichannel Hitachi autoanalyzer, Hitachi, Roche, Vienna, Austria) as well as blood pressure (BP) and cyclosporine concentration or tacrolimus level (Behring Diagnostics, Vienna, Austria) were measured during period I and period II at least four times per year. The mean values of each period were estimated and presented in Table 2.

The vascular diseases were classified in four stages: CVD: stage I: carotid artery stenosis <50%; stage II: stenosis >50% without clinical symptoms; stage III: stenosis >80% and/or clinical symptoms including transitoric ischemic attack (TIA); stage IV stroke in history. CHD: stage I: ischemic changes in ECG or angina pectoris during physical exercise; stage II: ischemic changes in ECG or angina pectoris at rest; stage III: enzymatic infarction and/or angioplasty (dilatation, stent implantation) or bypass surgery; stage IV: myocardial infarction in history. PVD: stage I: mediasclerosis or ankle/brachial pressure index 1.0–0.7; stage II: ankle/brachial pressure index <0.7 without symptoms; stage III: ankle/brachial pressure <0.7 with pains; stage IV: ischemic ulceration or necrosis requiring amputation.

Table 1. Baseline clinical data, vascular risk factors and prevalence of vascular diseases of patients prior to simultaneous pancreas kidney transplantation (SPKT) and kidney transplantation alone (KTA).

	SPKT	KTA
Age (years)	35 ± 5*	43 ± 9*
Female:male	7:5	7:3
BMI	23 ± 2	23 ± 3
Diabetes (years)	19 ± 3*	21 ± 4*
HbA1c (%)	7.9 ± 1.2	7.7 ± 1.2
C-peptide (ng/ml)	0.06 (0.0–0.2)	0.11 (0.0–0.2)
Dialysis (months)	6 ± 5**	24 ± 17**
Blood pressure (mmHg)		
Systolic	141 ± 9	142 ± 9
Diastolic	85 ± 6	84 ± 7
Antihypertensive agents (*n*)	2.2 (0–5)	2.1 (0–4)
Cholesterol (mmol/l)	6.3 ± 1.2	6.2 ± 0.8
Triglycerides (mmol/l)	2.1 ± 1.0	2.0 ± 1.0
Smoking (%)	25	20
Vascular diseases (stage I–IV)		
Cerebrovascular disease (%)	16	30
Coronary heart disease (%)	25	30
Peripheral vascular disease (%)	25	30

*$P < 0.01$, **$P < 0001$.

Statistical analysis

Data are presented as means (SD) or prevalence. For statistical analysis the chi-squared test was used for comparing differences between the groups, and the student's *t*-test for testing unequal variances. A *P*-value of <0.5 was considered significant.

Results

The mean HbA1c-values during the first 5 years after transplantation (period I) and the next 5 years until the end of the study (period II) were 5.7 + 0.4 and 5.8 + 0.4% in the SPKT group, respectively, and

Table 2. Mean values of HbA1c, fasting blood glucose (FBG), blood pressure, serum lipids and prevalence of cigarette consumption after transplantation during the first 5 years (period I) and the second 5 years (period II) after transplantation.

	Pancreas and kidney		Kidney alone	
	Period I	Period II	Period I	Period II
HbA1c (%)	5.7 ± 0.4**	5.8 ± 0.4**	7.4 ± 0.8**	7.6 ± 0.9**
FBG (mmol/l)	5.7 ± 1.1*	5.6 ± 0.8*	7.5 ± 1.8*	7.7 ± 0.8*
Blood pressure (mmHg)				
Systolic	137 ± 12	136 ± 14	138 ± 10	137 ± 11
Diastolic	83 ± 7	84 ± 6	84 ± 7	85 ± 8
Cholesterol (mmol/l)	6.1 ± 1.1	6.2 ± 1.3	6.3 ± 1.4	6.2 ± 1.1
Triglycerides (mmol/l)	1.3 ± 0.4*	1.4 ± 0.5*	2.2 ± 0.9*	2.3 ± 0.6*
Smoking (%)	25	16	20	20
Cyclosporine dose (mg/kg/day)	0.073 ± 0.037	0.53 ± 0.02.2	0.063 ± 0.046	0.041 ± 0.21
Prednisolone dose (mg/day)	7.5 (0–15)	0.5 (0–5)	7.5 (0–15)	2.5 (0–10)

*$P < 0.05$, **$P < 0.01$ (period I versus I and period II versus II).

7.4 ± 0.8% and 7.6 ± 0.9% in the KTA group, respectively. The differences between both groups and periods were significant ($P < 0.001$) as shown in Table 1. The cholesterol levels were about the same in both groups, triglyceride levels were lower in patients with SPKT (1.3 ± 0.4% and 1.4 ± 0.5%) than in patients with KTA (2.2 ± 0.9 and 2.3 ± 0.6 mmol/l, $P < 0.05$). The data of the vascular risk profiles in both patient groups during both periods of observation are summarized in Table 2. Systolic BP was similar in both groups over the entire observation period. All data of the vascular risk profile during both periods of observation are summarized in Table 2.

Five years after transplantation, the prevalence of vascular diseases (stage I–IV) was not significantly different between both groups. In the SPKT group the prevalences of CVD, CHD and PAV were 33%, 41% and 41%, respectively. In the KTA group the prevalence of CVD, CHD and PAV were 40%, 50% and 50%, respectively. Ten years after transplantation, at the end of the study, the prevalence of vascular diseases was higher in the patients with KTA. In the SKPT group the prevalence of vascular diseases (stage I–IV) was 41% for CVD, 50% for CHD and 50% for PAV, and in the KTA group 80% for CVD, 90% for CHD and 80% for PAV (NS). The overall frequency of the vascular complications i.e. myocardial infarction (16% vs. 50%), stroke (16% vs. 40%) and amputations (16% vs. 30%) was significantly lower in the patients with SPKT than compared within the patients with KTA ($P < 0.05$). The prevalence of vascular diseases stage I–II and stage III–IV 5 years as well as 10 years after transplantation is shown in Figs 1–3.

The prevalence of interventions in history at the end of the study was higher in the patients with KTA. Intervention in the legs was performed only once in the KTA group. Prevalence of interventions in the coronary arteries

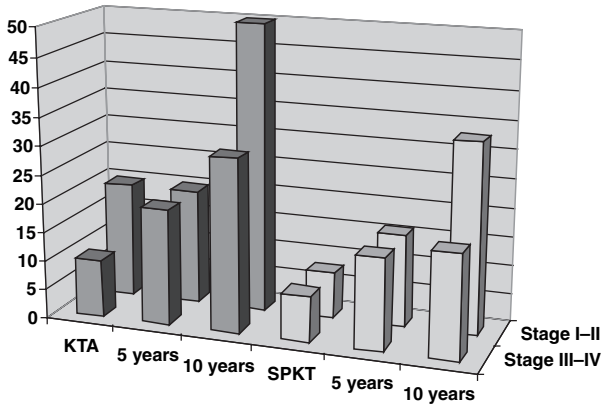

Figure 1 Prevalence of moderate (stage I–II) and severe (stage III–IV) coronary heart disease (CHD) before, and 5 and 10 years after simultaneous pancreas and kidney transplantation (SPKT) and kidney transplantation alone (KTA), respectively.

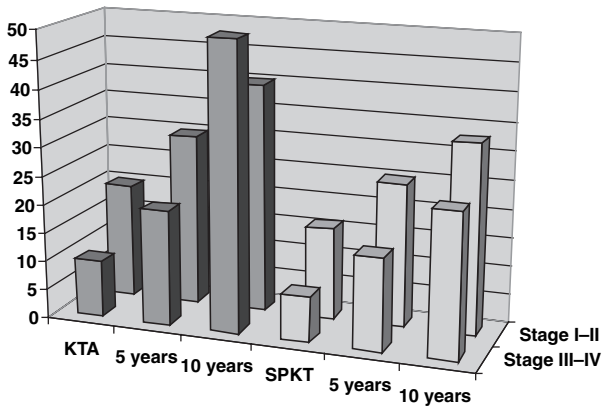

Figure 2 Prevalence of moderate (stage I–II) and severe (stage III–IV) cerebrovascular disease (CVD) before, and 5 and 10 years after SPKT and KTA, respectively.

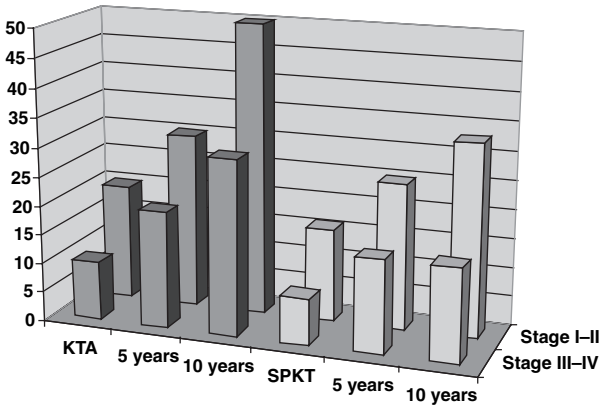

Figure 3 Prevalence of moderate (stage I–II) and severe (stage III–IV) peripheral vascular diseases (PVD) in the legs before, and 5 and 10 years after PSKT and KTA, respectively.

was 40% in the KTA group versus 25% in the SPKT group. The 10-year patient survival in patients with SPKT was not significantly different to the patients with KAT (83% vs. 70%), however it has to be mentioned that the patients in both groups were selected for 5 year functioning grafts at the start-initiation of the study. During the observation period three patients with KTA died because of myocardial infarction ($n = 2$) and sepsis ($n = 1$), two patients with SPKT died because of tuberculosis ($n = 1$) and sepsis ($n = 1$). The body mass index (BMI) was similar in both groups and at each period of observation.

Discussion

About 10 years ago the progression of macro-vascular diseases in patients after SPKT was controversially discussed in the literature. Several small series studies reported a high incidence of leg amputations after successful SPKT ranging from 10% to 23% [13,15]. In a larger study Kalker *et al.* [16] showed 19% incidence of lower extremity amputations in those patients. Two further studies compared the progression of PVD in SPKT patients with that of KTA patients [10,13]. In the one study the incidence of peripheral vascular complications in SPKT patients was even higher than in KTA patients. In the other study this incidence was similarly reported in both patient groups, although blood glucose levels were normal in the SPKT patients.

Recently the progression of coronary atherosclerosis was compared in SPKT patients who's pancreas graft was functioning or had failed. In this study coronary angiography was used. A mean follow-up of 3.9 years evidence emerged that the progression of coronary atherosclerosis was reduced in patients with a functioning pancreas graft compared with those who's pancreas graft had failed [12]. Further recent studies seem to confirm this finding that a better cardiovascular outcome of patients with SPKT was observed [13,17]. However, most of those studies investigated the efficacy of SPKT on preventing the progression of cardiovascular disease during a relatively short observation period.

In a study by Fioretto *et al.* [8] it was demonstrated that a reversal of microangiopathic lesions is observable only after more than 5 years of normoglycemia. Thus, it may be assumed that the reduction of clinical relevant macrovascular pathology following successful SPKT requires several years of normoglycemia, too. In an earlier study the progression of macrovascular diseases during the first 5 years was found similar in SPLT and KTS patients. The prevalence of CVD, CHD and PVD was found to be approximately the same after 5 years, blood glucose and triglyceride levels were found normalized in SKPT patients, in contrast to KTA patients. In our study, only patients with functioning grafts for at least 5 years, a significant difference between the prevalence of vascular diseases in SKPT patients and KTA patients were observed. At the end of the observation period, i.e. after a second mean period of 5 years, the overall prevalence of all the investigated vascular diseases was lower in the SKPT group than in the KTA group. But this was not statistically significant. However, in regards to the vascular complications the overall frequency of myocardial infarction, stroke and amputations were significantly lower in patients with SPKT compared to those with KTA ($P < 0.05$). Based on these results we would like to assume that SKPT with diabetic patients exhibits the potential to slow the progression of clinical relevant macroangiopathy compared to diabetic patients with only KTA. But this vascular protective effect after SKPT can be observed only onwards after 5 years of pancreas graft survival. However, it has to be mentioned that patients with SPKT were on maintenance dialysis for a significantly shorter time period than those treated with KTA, i.e. 6 months versus 24 months. It is well known from the literature that duration on maintenance dialysis represents an important risk factor for the progression of atherosclerosis and eventually for poor outcome, too [18]. Thus, one might argue that our SKPT patient group was perhaps healthier than our KTA group. However, according to our investigations the prevalence and the severity of macrovascular diseases before transplantation were not significantly different in both patient groups.

The long-term effect of SPKT on the progression of macroangiopathic diseases can be explained by better metabolic control. In our study the patients with SPKT had near normal blood glucose levels and significantly lower triglyceride concentrations than prior to transplantation. The mean levels of cholesterol were slightly

elevated in both groups. Our data are in accord with results of earlier studies showing comparable cholesterol levels after SPKT and KTA in patients with end-stage renal disease [19,20]. Additionally, in a study patients with SPKT showed elevated HDL-cholesterol which could be explained by low postprandial triglyceride levels resulting from a high activity of lipoprotein lipase [21]. This improved lipid profile in postdiabetic SPKT patients may counteract the atherosclerosis risk of long-lasting diabetes. In addition, peripheral hyperinsulinemia because of segmental pancreas transplantation with systemic drainage and exocrine diversion to the bladder may contribute to atherosclerosis by stimulating vascular smooth-muscle growth and arterial wall lipid deposition [22]. The negative lipid effect of cyclosporine can be avoided by using tacrolimus which is known to impair lipid metabolism [23] The influence of hyperinsulinemia may be reduced by using steroids for only few weeks. The pancreas transplantation with portal drainage may also lead to a lower insulin resistance and to a more effective prevention of the progression of macrovascular diseases in patients with SPKT.

In earlier studies it has been reported that hypertension may represent a main risk factor for atherosclerosis in patients with SPKT and KTA, and that hypertension in these patients is associated with cyclosporine therapy [24]. In our study the mean BP values were moderately increased in both groups, with comparable high doses of cyclosporine in both groups, too. The prevalence of smokers and patients with angiotensin converting enzyme (ACE)-inhibitor therapy was similar in the two groups of patients. In addition, the dosage of steroids was slightly different in both groups but difference was not significant. The BMI was identical in both groups before transplantation as well as during the observation period.

Several studies have shown that in type 1 diabetic patients below 50 years of age the long-term patient survival can be improved by SPKT although the simultaneous transplantation is associated with an excess initial morbidity [2,25,26]. In our study the 10-year patient survival rates tended to be higher in the SPKT group compared with the KTA group but the difference did not reach statistical significance.

From our findings we conclude that the progression of macro-vascular diseases is reduced in diabetic patients with SPKT in comparison with recipients of KTA, however, this effect will be significant not earlier as 5-year functioning pancreas graft. This vascular protecting effect of SPKT can only be observed after a longer period of pancreas graft function. An impact on patient survival is likely, in recent studies the patient survival was significantly higher in patients with SPKT in comparison with subjects with KTA [19]. In a recent study a substantial reduction in mortality was seen 10 years after successful SPKT (25). The authors assumed that the decrease in mortality after SPKT was mainly because of the beneficial effect of long-term normoglycemia. The recipients of kidney graft alone have usually hyperglycemia and hypertriglyceridemia as atherosclerotic risk factors [18]. In our study the patients with KTA had significantly higher levels of blood glucose and triglycerides than did those with SPKT; the serum cholesterol levels were moderately elevates in both cohorts. During the whole period of observation the mean BP values were similarly elevated in both group of our patients, but during the first 3 months after transplantation the BP was transiently higher in the group with SPKT. One reason for the increased risk for atherosclerosis during the first 5 years after transplantation also in patients with SPKT may be the higher administered cyclosporine doses in the patients with SPKT. In several studies persisting hypertension in end-stage renal disease after successful transplantation was found to be associated with cyclosporine therapy [27].

In summary, we have demonstrated that after more than 5 years of functioning pancreas graft the progression of macrovascular diseases is significantly reduced in diabetic patients with SPKT compared to recipients of KTA.

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