OUTCOME OF SECOND PANCREAS TRANSPLANTATION IN PATIENTS WITH PREVIOUS SIMULTANEOUS KIDNEY AND PANCREAS TRANSPLANTATION COMPARED TO PATIENTS WITH PREVIOUS KIDNEY ALONE TRANSPLANTATION

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Abstract- There had been few if any study for second pancreas transplant outcome and consequences in patients with simultaneous kidney pancreas transplant after failure of the first pancreas allograft. The aim of this study was to compare the patient and graft survival and clinical outcomes and complication of the second pancreas transplant in patients with simultaneous kidney pancreas, compared with pancreas after kidney transplantation in patients with no history of previous failed pancreas graft failure. Two groups of patients, patients with simultaneous kidney pancreas transplantation with pancreas graft failure (11 patients) and kidney transplant patients with no history of previous pancreas transplant having first pancreas transplantation (6 patients) were statistically compared. Immediate and short time difference in survival rate between group 1 and group 2 was 63% and 33%, respectively. The difference was attributable to more vascular thrombosis ending in graft loss in group 1, but this dose not achieve a statistical significance (P = 0.7); although long term survival rate difference was more evident and significant (P = 0.002). The only other statistically difference found between two groups was the donor's age with a P value of 0.02, in favor of the patients in group 2, who have received grafts from younger donors. The long term pancreas graft survival rate in patients with the history of previous pancreas transplantation in the setting of SKP is worse than pancreas graft survival in previously kidney transplanted patients, receiving their first pancreas in pancreas after kidney setting.

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INTRODUCTION

Historically the clinical acceptability of pancreas after kidney transplantation has been controversial because of relatively high acute rejection rate when compared with the more commonly performed simultaneous pancreas-kidney transplantation, (1, 2) although, recent studies have shown acceptable graft and patients survival rate in pancreas after kidney (PAK) transplantation (3, 4). To authors knowledge, there had been few if any study for second pancreas transplant outcome and consequences in simultaneous kidney pancreas (SKP) transplant

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patients after failure of the pancreas allograft, receiving another pancreas in the setting of PAK transplantation

Because of the prolongation of the kidney allograft survival and the more probability of the pancreas loss after SKP transplantation (5) an ever increasing portion of these patients would be candidate for the second pancreas transplantation. The aim of this study was to compare the patient and graft survival and clinical outcomes and complication of the second pancreas transplant in SKP patients, compared with PAK in patients with no history of previous failed pancreas graft failure.

MATERIALS AND METHODS

Setting and design

This study involved all patients undergoing pancreas transplantation after kidney transplantation in the hospital HEH Lyon France between October 1994 and October 2004.

In the beginning 21 patients entered this study: 14 patients with the history of the previous failed pancreas transplantation, either SKP (12 patients) or PA (2 patients), and 7 patients with no history of pervious pancreas graft attempt after kidney transplantation. Two patients with the history of pancreas alone (PA) transplantation and one patient in the SKP group who had the history of the second pancreas graft failure, after SKP, were omitted from the study. One patient was not followed and therefore also omitted. Then the patients were divided in two groups; group 1: SKP transplantation patients with pancreas graft failure (11 patients) and group 2: kidney transplant patients with no history of previous pancreas transplant (6 patients).

Data Collection

Demographic and multiple clinical outcomes from an established PTX data base were collected and confirmed via medical record review. Demographic data included age, body mass index, gender, duration of diabetes mellitus, history of coronary artery disease and arterial hypertension (Table 1), modality of dialysis before kidney transplantation or pre-emptive kidney transplantation, history of biopsy proved acute rejection in transplanted kidney before PAK transplantation (Table 2), cold ischemic time, techniques of surgery pancreas, (Table 3), transplantectomy in 48 hours after pancreas PTX, and re-operation in the first week after pancreas transplantation (Table 4), induction immunosuppression (Table 7).

Outcome information included as well as patient and graft survival rates (Table 5), re-laparotomy within first week of PTX, incidence of histologic or clinical rejection, infections complications (Table 6), requirement of insulin in the first day (D1) of PTX, day of the insulin arrest and restart day of insulin (data not shown).

Markers of renal and pancreas allograft function were assessed at 3, 6, 12 months and afterward yearly for creatinine, amylase, fasting serum glucose, C-peptide; insulin after oral stimulated hyperglycemia, haemoglobulin A1c levels (data not shown). Pancreas allograft loss was defined as death with functioning pancreas allograft, the requirement for scheduled daily insulin therapy, or transplant pancreatectomy.

Table 1. Demographic informations

Characteristic	Group 1 (SKP) (n = 11)	Group 2 (KA) (n = 9)	*P* value
Age at pancreas after kidney transplantation (year)	47.42 ± 4.71	42.71 ± 4.89	NS
Sex distribution/Female	9.4	6.2	NS
BMI	%22.88 ± 2.08	%18.36 ± 3.2	NS
Arterial hypertension	9	4	NS
Coronary artery disease	4	2	NS
Time between beginning of IDD and PAK transplantation (months)	31.57	27.85	NS

Abbreviations: SKP, simultaneous kidney pancreas; KA, kidney alone; NS, not significant; BMI, body mass index.

Table 2. Kidney function informations

Function	Group 1 (SKP)	Group 2 (KA)	*P* value
Creatinine μMOL/L day of pancreas transplantation	121.07 ± 33	119.28 ± 29.88	
Pre-kidney transplant dialysis modality (haemodialysis/peritoneal dialysis)	10.1	5.0	NS
Preemptive kidney transplantation	2	3	NS
History of acute rejection in the kidney before PAK transplantation (biopsy proved)	2	1	NS

Abbreviations: SKP, simultaneous kidney pancreas; KA, kidney alone; NS, not significant.

Table 3. Surgical techniques and cold ischemic time

	Group 1 (SKP)	Group 2 (KA)	*P* value
Portal vein prolongation	9	4	NS
Arterial anatomosis of pancreas allograft primary Iliac artery/external or internal Iliac artery	11.2 External iliac artery	7.1 internal iliac artery	NS
Placement of pancreas allograft in right/left Iliac fossa	8.5	5.3	NS
Portal/systemic endocrine diversion	4.9	3.5	NS
Cold ischemic time (minutes)	775±166	725±130	NS

Abbreviations: SKP, simultaneous kidney pancreas; KA, kidney alone; NS, not significant.

Immunosuppression regimens

With the exception of two patient in group 2 who received Simulect, all other patients received ALG for induction (Table 7) and in case of survival of the graft steroids, mycophenolate mofetil and cyclosporine were used for maintenance immunosuppression. It is necessary to mention that in three patients immunosuppression in the first day of pancreas transplantation included azathioprine instead of mycophenolate mofetil, but in less than three months, with the availability of mycophenolate mofetil in late 1995, azathioprine was substituted by mycophenolate mofetil.

Statistical analysis

Data are reported as mean +/-standard deviation. Bivariate analysis was performed by the Students *t* test for continuous data and Fisher's exact test for categorical data. A *P* value less than 0.05 was considered significant.

Table 4. Early re-operations

	Group 1 (SKP)	Group 2 (KA)	*P* value
Re-operation in the first week after PAK transplantation	6	2	NS
Pancreas transplenectomy in the first 48 hours after transplantation because of vascular thrombosis	8	1	< 0.05

Abbreviations: SKP, simultaneous kidney pancreas; KA, kidney alone; NS, not significant.

Table 5. Three months, 6 months and overall Pancreas graft survival rate

Survival rate	Group 1 (SKP)	Group 2 (KA)	*P* value
Pancreas graft survival in the first 3 months after transplantation	5 938.46%)	5 (62.5%)	> 0.1*
Pancreas graft survival in the first 6 months after transplantation	4 (30.76%)	3 (37.5%)	> 0.1*
Overall pancreas graft survival in the last follow up	3 (23.07%)	3 (37.5%)	> 0.1*
Overall loss of pancreas allograft due to vascular thrombosis	8.13 (73.44%)	1.8 (16.66%)	0.04†

Abbreviations: SKP, simultaneous kidney pancreas; KA, kidney alone; NS, not significant.
* log rank test
† Fisher exact test

Table 6. Pancreas graft acute and chronic rejection

Rejection	Group 1 (SKP)	Group 2 (KA)	*P* value
Acute rejection or acute on chronic rejection of the pancreas	2	1	NS
Chronic rejection of the pancreas	1	1	NS

Abbreviations: SKP, simultaneous kidney pancreas; KA, kidney alone; NS, not significant.

RESULTS

Baseline characteristics

Of the 162 PTX performed between December 1994 and December 2004 in HEH hospital in Lyon France, 24were pancreas after kidney transplantation. 14 of these PTX were performed in patients with the history of previous SKP transplantation with failed pancreas graft but still functioning kidney allograft, and in two patients second PAK transplant after the failure of the primary pancreas transplantation, was performed;. Then patients with SKP transplant and pancreas graft failure and patients with only kidney transplantation and no previous pancreas transplantation attempt entered this study and accordingly named group 1 and group 2. The demographic and transplant related characteristics are listed in Table 1. As can be seen; regarding age, sex distribution, BMI, history of arterial hypertension, coronary artery diseases and lag of time between commencement of diabetes mellitus and last pancreas transplantation there is no statistically significant difference between two groups. Transplant characteristics of the previous kidney transplant, modality of dialysis or preemptive kidney transplantation, history of acute rejection of the kidney before PAK transplantation, creatinine in the first day of PAK transplantations a marker of kidney function are summarized in Table 2 and again there is no significant statistical difference. Pancreas transplant characteristics: Cold ischemic time, portal or systemic endocrine drainage, technique of surgery regarding; prolongation of portal vein, arterial and venous anastomosis, right or left iliac fossa placement of the pancreas transplant (Table 3); and re-operation in the first week after operation, pancreas transplantectomy in the first 48 hours after operation (Table 4), again shows no statistically significant difference between two groups.

Mortality and graft failure

During the follow up period there were no patient death or renal allograft failure before loss of pancreas in either of two group. At the last follow up the overall pancreas transplant survival for the patients with previous SKP transplantation and pancreas graft failure, who have had a second pancreas graft in the setting of PAK transplantation (group 1), was 27, 27% and for the patients with the history of only previous kidney transplantation who have had received the first pancreas graft in the setting of PAK transplantation (group 2), the pancreas graft survival was 50% (P = 0, 002).

The survival of the pancreas graft in two groups in three and six months after transplantation was 63, 633%, 83, 33% (P = 0.7) and 54, 54%, 50% (P = 0.1) respectively with no significant statistic difference (Table 5). The cause of loss of pancreas in the 3 months after transplantation in all cases was vascular thrombosis, 4 cases in group 1 and 1 case in group 2, all occurring in the immediate 48 hours after transplantation. The overall cause of loss of the pancreas in group 1 was; vascular thrombosis in 6 patients; chronic rejection in 1 patient; acute

Table 7. Immunosuppression in the first day of transplantation

Immunosuppression	Group 1 (SKP)	Group 2 (KA)
Simmulect/mycophenolate Mofetil/Cyclosporin/ Steroids	0	2
ALG/ Azathioprine/ Cyclosporine/ Steroids	3	1
ALG/Mycophenolate Mofetil/Cyclosporine/ Steroids	10	5

Abbreviations: SKP, simultaneous kidney pancreas; KA, kidney alone; NS, not significant.

vascular rejection on chronic rejection in the last patient, and in group 2 the pancreas allograft was lost in one patient after transplantectomy because of PTLD (post transplant lymphoma) in the allograft; in one other patient the cause of loss of pancreas was immediate vascular thrombosis and the last patient lost his pancreas after acute rejection. All cases of vascular thrombosis were detected by colour Doppler sonography and confirmed by either arteriography or anatomopathology after transplantectomy. In case of the presence of another pathology, like rejection, with vascular thrombosis the other pathology was accepted as the cause of graft loss. Of the 11 cases of pancreas graft failure in two groups, vascular thrombosis, was the culprit in 6 (75%) cases in the group 1 and 1 case (33%). in group 2, (P = 0.215). The overall loss of pancreas graft because of thrombosis was about of 11 (54.54%) PAK transplantation in group 1 and one out of 6PAK transplantation (16.66%) in group 2 (P = 0.16) (Table 5). By surveying the clinical records of the previous SKP transplantation in group 1 it became evident that in 5 out 6patients with the pancreas graft loss because of vascular thrombosis the cause of loss of pancreas after SKP had been also vascular thrombosis.

Acute rejection

The incidence of biopsy proven acute rejection of the kidney before and after pancreas transplantation was comparable between two groups (Table 2).

Regarding the pancreas allograft because there had been no systematic biopsy the pancreas function was regularly monitored by oral stimulated hyperglycemia test and amylase, lipase measurement. All the cases of pancreas allograft dysfunction in two groups had a definitive clinical and subsequently, except one case anatomopathological diagnosis after transplantectomy. Again there is no statistically significant difference in this regard between two groups

Surgical Technique

All pancreas allografts were placed intra-abdominally with enteral drainage for the exocrine secretions.

The major selection criteria were donor quality as defined by young age (less than 40) absence of prolonged periods of low blood pressure, and no abnormality in serum lipase. In spite of this, there was a significant difference, between donor's mean age in group 1 and group 2; 28.45 and 20.66 years respectively (P = 0.02) in favour of patients receiving their first pancreas after kidney in group2. Final inspection of the pancreas at the time of transplantation on the back table ensured a high-quality donor pancreas, with minimal fat or edema. The mean donor age in groups1and2 was 28.45 and 20.66 respectively. No attempt was made to match human leukocyte antigen types between the donor and recipient.

Morbidity

There was 6 reoperation in the first week after transplantation in group1, four for pancreas transplantectomy, and two for intra-abdominal hematoma and haemorrhage, in comparison there was three cases of reoperation in group2; 1 for pancreas transplantectomy and two other ones for intra-abdominal haemorrhage. There was a 18% incidence of CMV infection in group 1compared with 16%in group 2. One patient in group 2, four months after transplantation was diagnosed with, post transplant lymphoma inflicting the pancreas, there was no other cases of PTLPD in either two groups. Concerning the incidence of carcinoma only one patient in group1 was inflicted with basal cell carcinoma (BCC).

Graft function

Several markers of pancreas and renal allograft function were assessed serially throughout post-transplant follow-up. There was no difference between groups with regard to serum creatinine in the first day of transplantation and subsequent follow-ups, 3 months, 6 months and yearly afterwards.

In the patients with functioning pancreas graft , there was no difference in haemoglobin A1c (Table 4), fasting serum glucose , or C peptide levels between the two groups in 3, 6, months after transplantation and subsequent yearly follow-ups (data not shown).

DISCUSSION

Although due to the relative smallness of the two groups, generalization about the results is difficult there are some facts that can be mentioned. This is a single centre ten years experience with the same surgical and nephrology teams that eliminates the possible centre effect. This fact that in the last follow up the survival rate of the second pancreas graft in SKP transplant patients with loss of previous pancreas graft (group 1), was 27.27% compared with 50% in previously kidney alone transplant patients who have received their first pancreas graft in the setting of PAK transplantation (group 2), $P = 0.002$ in spite of relative smallness of two groups is remarkable and shows a significant statistical difference in survival between two groups. The fact that that 6 out of 8 cases of pancreas graft loss in group 1were because of vascular thrombosis and four of these vascular thrombosis have occurred immediately after transplantation , compared with only one graft loss after vascular thrombosis in group2, ($P = 0.16$), although not reaching the cut-off line of statistical significance, is clinically significant. When comparing the cause of loss of the first and second pancreas graft, in group 1, it became evident that in 5 cases, in both first (SKP transplantation) and second, pancreas transplant attempt, vascular thrombosis, has been the cause of immediate graft loss. The predictive value of vascular thrombosis in first transplantation, for loss of the second one, for the same reason, was 62% that is again noticeable. When controlling both groups , regarding surgical and technical factors influencing occurrence of vascular thrombosis , prolongation of portal vein had a significant association with vascular thrombosis in all patients in two groups (P =0.02), but again no difference in this regard between two groups was found. These results are comparable with the results reported by others. (6) Immediate and short time, three months, difference in survival rate between group1 and group 2, 63, 63% and 83, 33%was respectively, all the difference attributable to more vascular thrombosis ending in graft loss in group1, but this clinically important fact, dose not achieve a statistical significance (P =0.7) although long term survival rate difference, is more evident and significant ($P = 0.002$). The only other statistically difference found between two groups is the donor's age with a p-value of 0.02, in favour of the patients in group 2, who have received grafts from younger donors. Again perhaps due to this difference , the long term survival rate had been in favour of group1 ($P = 0.02$) although directly translating this statistical difference into clinical significance is doubt full, this and other not thoroughly explained facts justifies, a more large scale investigation, searching for other probable causes.

Conflict of interests

We have no conflict of interests.

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