

Simultaneous pancreas-kidney transplantation: Early complications and long-term outcomes – a single-centre experience

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Abstract

Introduction: This study aimed to assess the prevalence and severity of complications after simultaneous pancreas-kidney transplantation (SPKT) and to evaluate its influence on both grafts' long-term results.

Methods: This was an observational, retrospective study including 39 consecutive SPKT cases from 2000–2018. Complications were classified into kidney-related and pancreas-related. The severity of complications was assessed using the modified Clavien-Dindo scale. Kaplan-Meier curve analysis and log-rank tests were used. Cox regression was performed for the multivariate analysis.

Results: All 39 recipients had long-term type I diabetes. Twenty-one (53.8%) patients suffered a Clavien-Dindo \geq IIIa complication. Most complications were pancreas-related, with 17 (43.6%) patients suffering from one. Kidney-related major complications were seen in 11 (28.2%) patients. Patient survival at one, five, and 15 years was 89.7%, 87.1%, and 83.9%, respectively; kidney survival was 87.1%, 81.4%, and 73.6%, respectively; and pancreas survival was 76.9%, 71.3%, and 72%, respectively. Pancreas graft survival was influenced by the presence of major postoperative complications; patients and kidney graft survival were not.

Conclusions: Complications after SPKT influence pancreas graft survival. Despite the high rate of complications, our results suggest that patients' and kidney graft survival may not be affected by complications.

Introduction

Patients with end stage renal disease (ESRD) due to type I diabetes mellitus (DM) have a very poor prognosis without a kidney transplantation (1). Simultaneous pancreas-kidney transplantation (SPKT) is the gold standard for these patients (2). Pancreas transplantation is the only therapy that restores normal glucose metabolism in these patients. SPKT not only improves renal disease outcomes, but also other diabetes-related complications such as vascular and neurological complications (3). SPKT can also be performed in selected patients with type 2 DM with similar results to type 1 patients (4), although the 2020 KDIGO guideline only recommended it for type 1 DM, with no suggestions for type 2 DM (5). SPKT has an extremely high rate of surgical complications and surgical-related mortality (6-12). Although there is a trend towards lower complications rates after SPKT (6), most series report relaparotomy rates that vary from 23% (7) to a 57% (6). Most of these complications are related to the pancreas. In fact, pancreas transplantation has the highest rate of complications among all the solid organ transplants (8). These complications may have an impact on graft long-term outcomes. It seems logical to think that graft thrombosis or extensive bleeding that needs to be evacuated in an operating room, sometimes with hemodynamic instability, will have an impact on graft outcomes. In fact, thrombosis is commonly managed with graft nephrectomy or pancreatectomy. Some studies describe the negative influence of these complications on pancreas graft long-term outcomes (7-11). However, its influence on kidney graft survival remains unclear, with inconsistent results from published studies (7-12).

The aim of our study was to evaluate the influence of postoperative complications on the long-term survival rates of both grafts and patients.

Methods

This was an observational retrospective study including all patients who underwent a SPKT in our centre between January 2000 and December 2018.

The surgical technique was identical in all patients. Pancreas transplantation was performed by two general surgeons and kidney transplantation was performed by three different urologists. All pancreases were transplanted into the right iliac fossa. Vascular anastomosis was performed using the common iliac artery and vein, and exocrine drainage was performed by anastomosing the graft's duodenum to the recipient's ileum. Kidney grafts were placed into the left iliac fossa with a second incision. We used the external iliac artery and vein for vascular anastomosis. Ureterocystostomy was performed by the Lich-Gregoir technique, using a ureteral stent. Antibiotic prophylaxis was given before anaesthetic induction, generally with amoxicillin/clavulanic acid. The immunosuppression protocol was the same for all patients, consisting of basiliximab induction followed by maintenance with

tacrolimus, mycophenolate mofetil and prednisone. Thymoglobulin induction is reserved in our centre for hyperimmunised patients. All patients received thromboprophylaxis with low-molecular-weight heparin, starting 12 hours after the surgery. During the first 24 hours, a CT scan or a Doppler ultrasound was performed in order to rule out early complications, particularly vascular complications.

Complications during the first 90 days after the procedure were registered and divided into kidney and pancreas-related complications. Kidney-related complications included delayed graft function (DGF), graft rejection, arterial or venous thrombosis, arterial stenosis, bleeding, ureteral stenosis, urinary fistula, lymphocele, infectious complications and wound dehiscence. Pancreas-related complications included delayed endocrine graft function, graft rejection, arterial or venous thrombosis, intestinal fistula, bleeding, infectious complications and wound dehiscence. Kidney DGF was defined as the absence of improvement in kidney function during the first week after transplantation. Delayed endocrine graft function was defined as the need for insulin therapy with at least half the dosage needed before transplantation, during the first week after transplantation. Severity of complications was classified according to the modified Clavien-Dindo scale (13,14). For the analysis, we divided complications into minor (Clavien I-II) and major (Clavien \geq IIIa) complications. When a patient developed more than one complication, the higher-grade complication was taken into account.

For graft survival analysis, the moment of kidney graft loss was defined as the return to dialysis, and pancreas graft failure as returning to insulin requirements as previous to the transplantation. Graft survival was censored for patient death with a functioning graft, and patients with no record of death or graft failure were censored at the date of last follow-up. Statistical analysis was performed using IBM SPSS Statistics 23. Quantitative variables were compared using Student's t-test. For the comparison of qualitative variables, the chi-squared test was used. Survival analysis was performed using the Kaplan-Meier method and log-rank test. Cox proportional hazard models were used for multivariate analysis.

Results

A total of 39 patients underwent a SPKT in our centre during the time examined. The mean age of the recipients was 35.91 ± 5.96 years. Twenty-two (56.4%) of them were male. All recipients had long-term type I diabetes, with a mean of 23.54 ± 5.66 years from diagnosis. Ten (25.6%) of the patients were in the pre-emptive stage, and the rest of them were on substitute treatment, either haemodialysis (56.4%) or peritoneal dialysis (17.9%). All kidneys and pancreas grafts came from brain-dead donors. No donors with expanded criteria were used. The most common cause of death in donors was traumatic brain injury. The mean donor age was 27.67 ± 9.57 SD years. Median pancreas cold ischemia time was 4 ± 2.12 SD hours, although these data were missing for most of the patients (only 10 available). Median kidney cold ischemia time was 8 ± 3.01 SD hours. All donor and recipient characteristics can be seen in Table 1.

During the first three months, 21 patients (53.8%) suffered from a Clavien-Dindo \geq IIIa complication. The rate of Clavien-Dindo \geq IIIa complications was 43.6% (17) for pancreas-related complications and 28.2% (11) for kidney-related complications. The most frequent

complication for both grafts were infectious complications, most of them minor, with only one of these requiring surgical treatment. The most severe complications were bleeding, intestinal fistula and vascular thrombosis. All vascular thromboses led to graft loss. There were four transplant-related deaths, three of them secondary to pancreas complications, and one kidney-related. The type of complications, frequencies, and classifications following the modified Clavien-Dindo scale can be found in Table 2.

After the first three months, four patients underwent a relaparotomy for ureteral stricture. No other late transplant-related complications were registered.

Mean follow-up was 96.54 ± 78.94 months. Patient survival rates at 1, 5 and 15 years were 89.7%, 87.1% and 83.9%; kidney survival rates were 87.1%, 81.4% and 73.3%; pancreas survival rates were 79.9%, 71.3% and 72%, respectively. Patients and kidney graft survival rates were not significantly affected in those who suffered a major complication (Clavien-Dindo \geq IIIa), but there was an influence of major complications on the pancreas outcomes. Pancreas survival rates at 1, 5 and 15 years were 93.8%, 93.8% and 81.3% for patients who did not require a relaparotomy, and 57.1%, 52.4% and 45.8% for those who did ($p=0.009$). Kidney graft survival rates were 93.8%, 87.5% and 79.5%; and 76.2%, 76.2% and 68.6%, respectively ($p=0.873$). Patient survival rates for those without a major complication were 93.8%, 93.8% and 93.8%; these rates were 81.0%, 76.2% and 76.2% for patients who suffered from a Clavien-Dindo \geq IIIa complication ($p=0.099$) (Fig. 1).

Regarding kidney-related complications, the presence of a Clavien-Dindo \geq IIIa kidney-related complication showed no influence on patient survival ($p=0.676$), pancreas graft survival ($p=0.513$), or kidney graft survival ($p=0.837$) (Fig. 2).

Patients who suffered a Clavien-Dindo \geq IIIa pancreas-related complication showed significantly decreased pancreas graft survival ($p=0.016$), while there were no significant differences in kidney graft ($p=0.730$) and patients ($p=0.196$) survival (Fig. 3).

No individual complications or complications sorted by Clavien-Dindo grade revealed a statistically significant influence on survival rates in the multivariate analysis. Although there was a tendency towards worse pancreas survival in those patients who presented pancreatic major complications, these results were not significant [HR 2.42 (95% CI: 0.83-7.01), $p=0.1$].

Discussion

Complications after SPKT are an important concern, as the relaparotomy rate after the procedure is very high (15). Patients with chronic kidney failure due to type I diabetes do not have a good prognosis without some kind of transplantation, and SPKT is the gold standard in these patients (16).

An initial reduction in patient survival during the first three months compared to patients on the waiting list has been reported. After that, the relation reverses and one-year patient survival after SPKT is better than those on the waiting list (17). This initial decrease in survival is probably due to perioperative complications. Despite these, no study has shown a decrease in long-term patient survival rates for those patients who present major complications (7-11).

The majority of postoperative complications that require surgical treatment in the SPKT population are pancreas-related (8,18,19), which is consistent with our findings, as 28.2% of our patients suffered from a kidney-related major complication, whilst the rate was 43.6% for pancreas-related.

Some donor, recipient and transplant characteristics, such as donor age, cold ischaemia time and time on dialysis treatment have demonstrated an influence on the incidence of surgical complications (18,20-22). Patient selection becomes essential to decrease complications rates. For patients with a short life expectancy, the risk of complications does not outweigh the potential benefit (19). In our series, major complications after SPKT did not affect patient survival rates, although there was a tendency towards significance in those patients who suffered from any kind of major complication ($p=0.099$). No other previous study showed decreased patient survival in patients who required a relaparotomy (7-11). Postoperative complications after SPKT have been shown in most previous studies to have a negative influence on pancreas graft survival rates (7-10). These results are consistent with ours, as pancreas survival was influenced by the presence of surgical complications ($p=0.009$), and specifically by its pancreas complications ($p=0.016$). Kidney-related complications do not seem to influence pancreas graft survival ($p=0.513$). There were eight (20.5%) pancreas graft losses secondary to postoperative complications, five (62.5%) of them due to vascular thrombosis, two (25%) because of bleeding and the last one (12.5%) due to an intestinal fistula.

It is not clear whether pancreas graft loss influences kidney graft survival rates. Hill et al. (23) reported decreased kidney graft survival in patients with early pancreas graft failure (HR 2.08, $p=0.006$). These results were not confirmed by Das et al. (11), as neither kidney graft survival nor patient survival were influenced by pancreas graft loss. Similarly, the influence that major complications may have on kidney graft survival is not clearly established, with contradictory results in scientific reports. Banga et al. (7) found that patients with major complications during the first three months had decreased five-year pancreas survival (74% vs. 82%, $p=0.027$), but no differences were found in kidney survival (82% vs. 83% $p=0.412$). On the other hand, Campos-Hernandez et al. (12) found decreased five-year kidney graft survival among patients who had Clavien-Dindo \geq IIIb complications (81.8% vs. 97.3%, $p=0.001$). Similar results were found by Manrique et al. (9) and Steurer et al. (10). Neither of these studies separated pancreas-related from kidney-related complications. In our series, patients who presented a surgical complication (either pancreas- or kidney-related, or both of them) did not have a decreased kidney graft survival during follow-up. Of all patients who presented a kidney-related major complication during the first three months, one patient died due to massive haemoperitoneum after kidney graft nephrectomy performed for arterial thrombosis. There were no other patients or graft losses in this group.

The main cause of graft loss during the postoperative period was vascular thrombosis, most of them pancreatic. In fact, in our study, all arterial and venous thromboses resulted in graft loss. Although graft thrombosis rates have decreased over time, mainly because of changes to immunosuppressive protocols (10) and technical improvements (19), it is still the most important cause of graft loss. Pancreas grafts seem to be particularly prone to

thrombosis. It has been postulated that this could be because of an intrinsically low microcirculatory blood flow, which is based on collateral circulation (24,25). Kidney graft thrombosis seems to be related to atherosclerosis of the recipient iliac artery (26).

The limitations of the present study include its retrospective nature, the small number of patients and the fact that it was a single-centre study. Also, the period described is long, meaning that although surgical techniques and immunosuppressive prophylaxis have not changed, some perioperative care items not taken into account in this study may have been different. The long period described also means that follow-up periods of the patients are highly variable, as for some patients it was only two years while for others follow-up was as long as 18 years. Despite these limitations, our results are encouraging and show that, although complications after SPKT are common, they may not affect patient and kidney graft survival rates. Further research with prospective data and larger cohorts is needed to confirm these results.

DRAFT

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Figures and Tables

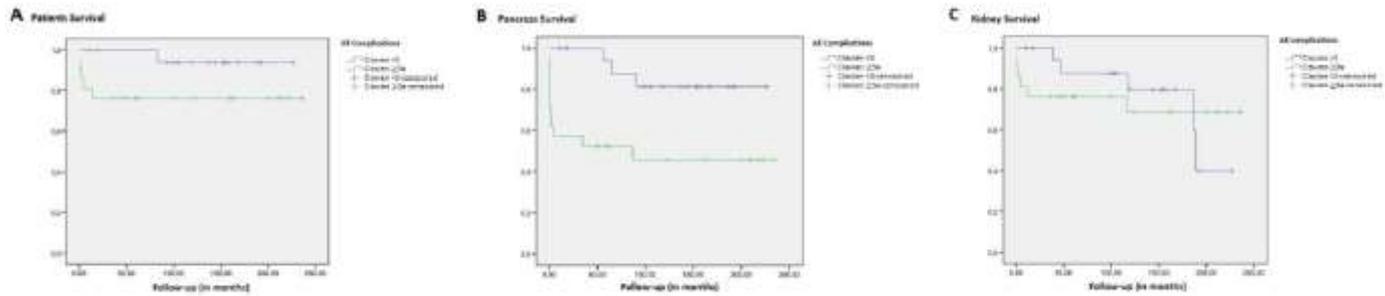
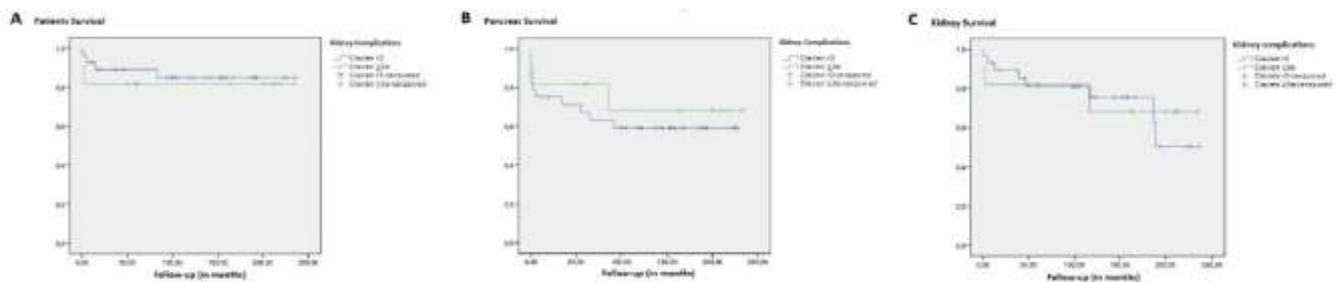
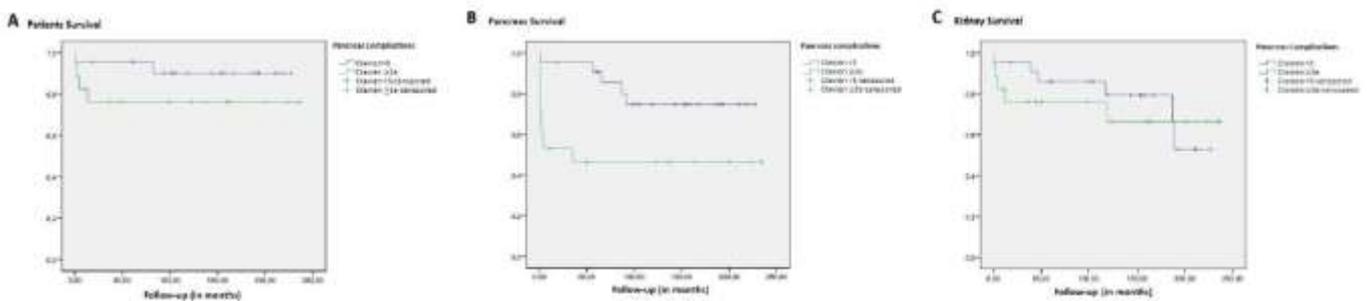
Figure 1. Influence of all complications on patients' (A) pancreas; (B) kidney; (C) graft survival rates.**Figure 2.** Influence of kidney-related complications on patients' (A) pancreas; (B) kidney; (C) graft survival rates.**Figure 3.** Influence of pancreas-related complications on patients' (A) pancreas; (B) kidney; (C) graft survival rates.

Table 1. Characteristics of SPKT recipients and donors (expressed by mean \pm SD, or number [rate])		
Donors characteristics		
Age		27.67 \pm 9.57 years
Gender	Female	14 (35.9%)
	Male	25 (64.1%)
BMI		24.48 \pm 3.7
Creatinine		0.77 \pm 0.27 mg/dL
Cause of death	Head trauma	22 (56.4%)
	Cerebrovascular/stroke	13 (33.3%)
	Anoxic brain injury	4 (10.3%)
Recipients characteristics		
Age		35.91 \pm 5.96 years
Gender	Female	17 (43.6%)
	Male	22 (56.4%)
BMI		22.30 \pm 3.9
DM time		23.54 \pm 5.66 years
Dialysis time		15 \pm 27.13 months
Dialysis type	No dialysis	10 (24.6%)
	Heamodialysis	22 (56.4%)
	Peritoneal dialysis	7 (17.9%)

BMI: body mass index; DM: diabetes mellitus.

Table 2. Kidney-related and pancreas-related 90-day complications according to the modified Clavien-Dindo classification											
Type of complication	Delayed graft function	Acute rejection	Arterial thrombosis	Venous thrombosis	Arterial stenosis	Ureteral stricture	Infection	Wound dehiscence	Fistula	Bleeding	Lymphocele
Kidney complications											
II	4	11					17			3	2
IIIa											1
IIIb					1				3	5	
IVa											
IVb			1							1	
Total	4 (10.3%)	11 (28.2%)	1 (2.6%)	0	1 (2.6%)	0	17 (43.6%)	0	3 (7.7%)	9 (23.1%)	3 (7.7%)
Pancreas complications											
II	1	5					12			8	
IIIa							1	3			
IIIb									1	6	
Iva			3	2					1	2	
Ivb									2	1	
Total	1 (2.6%)	5 (12.8%)	3 (7.7%)	2 (5.1%)	0	-	13 (33.3%)	3 (7.7%)	4 (10.3%)	17 (43.6%)	0