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Pancreas Transplantation : Towards Minimization of Technical Graft Loss

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Key words. Pancreas transplantation ; kidney transplantation ; combined transplantation.

Abstract. The objective of the study is to determine whether evolution in surgical techniques results in minimization of technical graft loss after simultaneous pancreas-kidney transplantation (SPKTx). Eighty consecutive patients with insulin-dependent diabetes mellitus and end-stage nephropathy, and who received SPKTx, were studied. Patient, pancreas and kidney survival at 5 years were 89, 84 and 84% respectively.
The porto-systemic venous anastomosis laterally to the arterial vessels resulted in exclusion of technical graft loss due to venous thrombosis. The switch from exocrine bladder drainage to enteric drainage lowered significantly the post-transplant surgical morbidity.
This series indicates that excellent short- and long-term survival can be obtained after SPKTx and this with a low peri-operative surgical morbidity.

Introduction

Successful simultaneous pancreas-kidney transplantation (SPKTx) provides an insulin-independent state with euglycaemia, normalization of various metabolic parameters and freedom from dialysis.

In addition to the improvement of patient's quality of life with greater personal, social and dietary freedom (than while on exogenous insulin) one of the favorable goals of pancreas transplantation is to try to halt the evolution of the secondary microvascular (diabetic nephropathy, neuropathy, retinopathy) and macrovascular complications (atherosclerotic cardiac and vascular disease), thereby prolonging a patient's life expectancy exceeding those of kidney transplants alone (1-3).

Although SPKTx is a relatively more invasive surgical procedure compared to kidney Tx alone, change in vascular technique and management of exocrine drainage have reduced the incidence of technical complications (4).

The introduction of two immunosuppressants, tacrolimus and mycophenolate mofetil, has resulted in reduced rates of rejection (5, 6).

We reviewed our center experience of SPKTx in type I diabetic patients mostly focusing on the evolution of surgical techniques and their impact on the results.

Materials and methods

From January 1992 until February 2007, 80 SPKTx in C-peptide negative type I diabetic patients with end-stage diabetic nephropathy were performed at the University Hospitals Leuven.

Actuarial patient and graft survival is analyzed in the two different time periods before and after modification of the venous vascular anastomosis technique (see below) with respectively 31 and 49 patients.
Study of morbidity is focused on surgical complications.

Results

1. *Demographic characteristics*

Pretransplant demographic data and organ characteristics are summarized in table I.

2. *Surgery* (Fig. 1)

A midline laparotomy is used. The pancreas is transplanted first in the right iliac fossa and the kidney second in the left iliac fossa.

Pancreas Tx. In 52.6%, the arterial supply to the pancreas allograft was assured by a donor aorta Carrel patch including the celiac trunk and the superior mesenteric artery. In the other cases (47.3%), several techniques were used to reconstruct the arterial blood supply : an end-to-side anastomosis of the splenic artery to the superior mesenteric artery, either directly (15.8%) or by using a bridge iliac artery graft (22.4%) ; a donor iliac bifurcation graft to perform an anastomosis of the donor internal iliac artery to the graft splenic artery and the donor external iliac artery to the graft superior mesenteric artery (9.2%).

An end-to-side anastomosis of the (reconstructed) graft arterial blood supply is performed to the recipient right common or external iliac artery. An end-to-side anastomosis of the graft portal vein to the recipient

Table I

Pretransplant demographic data and organ characteristics

Donor demographic characteristics		
Sex (M/F)		45/35
Mean age		27.7 yrs (13-49)
Mean weight		67 kg (43-95)
Mean BMI		22 (16-35)
Mean ICU stay		2 days (0-11)
Blood group		57% O ; 35% A ; 6% B ; 2% AB
Causes of death		61% CCT ; 33% CVA ; 6% other cause
Recipient demographic characteristics		
Sex (M/F)		44/36
Mean age		41.5 yrs (26-59)
Mean weight		65 kg (44-99)
Mean pretransplant dialysis time		19.1 months (1-180)
Mean pretransplant diabetes registration		329.0 months (10.5-1181.2)
Previous renal transplantation		n = 4 (1M/3F)
Procedure-related characterics		
Preservation solution		UW 100%
Mean cold ischaemia time	kidney	12.1 ± 2.1 hrs
	pancreas	10.4 ± 2.24 hrs
Mean second warm ischaemia time	kidney	35.14 ± 7.6 min
	pancreas	38.20 ± 8.47 min
Pretransplant comorbidity		
Cardiac disease	n = 29	36.3%
Peripheral vascular disease	n = 22	27.5%
Hypertension, disordered lipid status	n = 45	56.3%
Neuropathy / retinopathy	n = 72	90.0%

external iliac vein (*medially* to the iliac artery) was done in the first 31 cases ((38.8%) (first era until 1997)). In the last 49 patients (second era), this anastomosis has been performed on the common iliac vein *laterally* to the arterial vessels after thorough mobilization.

Exocrine drainage was realised with stapled anastomosis of the donor duodenal segment to the dome of the bladder in the first 45 grafts (56.3%). Enteric drainage with a side-to-side duodenojejunostomy has been performed in the last 35 cases.

Kidney Tx. The kidney transplant is attached to the left iliac vessels by using end-to-side venous and arterial vascular anastomoses. The ureter is anastomosed to the dome of the bladder by using extravesical ureteroneocystostomy (Lich-Grégoire). The kidney is "retroperitonealized" with the sigmoid colon.

3. *Perioperative management*

Current immunosuppressive regimen consists of simulect® day 1 and 4, FK506®, mofetil® and steroids. Patient details are summarized in table II.

Piperacillin/tazobactam and fluconazole are the routinely used antibiotics. Prophylaxis against pneumocystis carinii is with trimetoprim sulfamethoxazole. Patients at risk for CMV (cytomegalovirus) infection (D+/R- ; D+/R+ ; D-/R+) receive Acyclovir® (53.7%) or nowadays Gancyclovir® (40.0%).

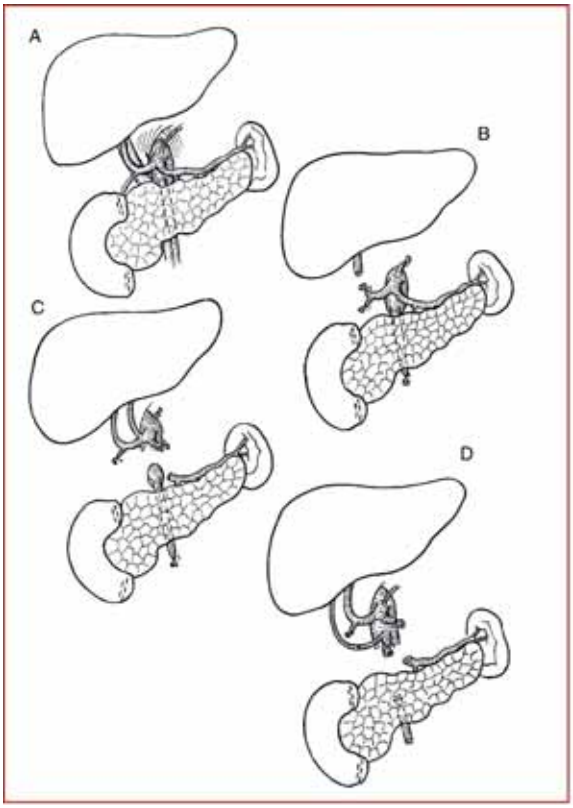
Continuous insulin infusion is used to "rest" the islets of the pancreas allograft and to achieve optimal blood glucose levels between 80 and 120 µg/dl immediately posttransplant. Somatostatine® (250 µg in shot ; 6 mg/24 hrs), aiming to lower exocrine secretion, is administered for 7 days to protect the enteric duodenojejunostomy.

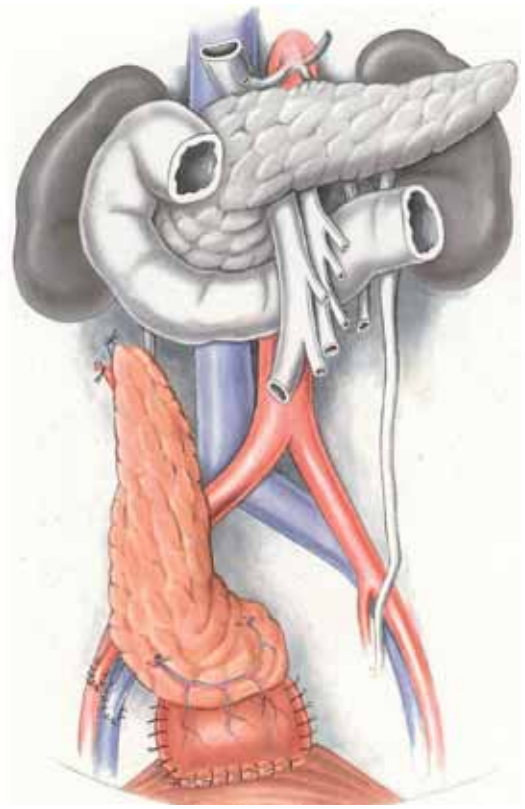
Low molecular weight heparine (subcutaneous Clexane® 20 to 40 mg daily), a stringent fluid balance to keep the central venous pressure at least 5 cm H2O and pneumoboots for lower leg venous compression are of primordial importance in thrombosis prophylaxis.

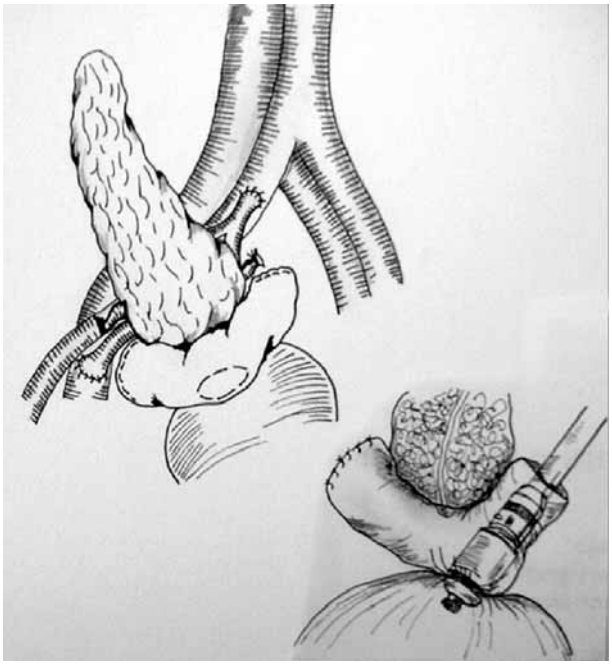
4. *Patient and graft survival*

The 1- and 5-year actuarial patient survival in the first era (n = 31, until 1997) was 97 and 88% respectively. The 1- and 5-year actuarial patient survival in the second era (n = 49, from 1997) is 95 and 89% respectively (Fig. 2).

Overall, twelve patients died with a functioning pancreatic allograft ; 3 of these with a non-functioning kidney due to chronic rejection. Causes of death are noted in table III.







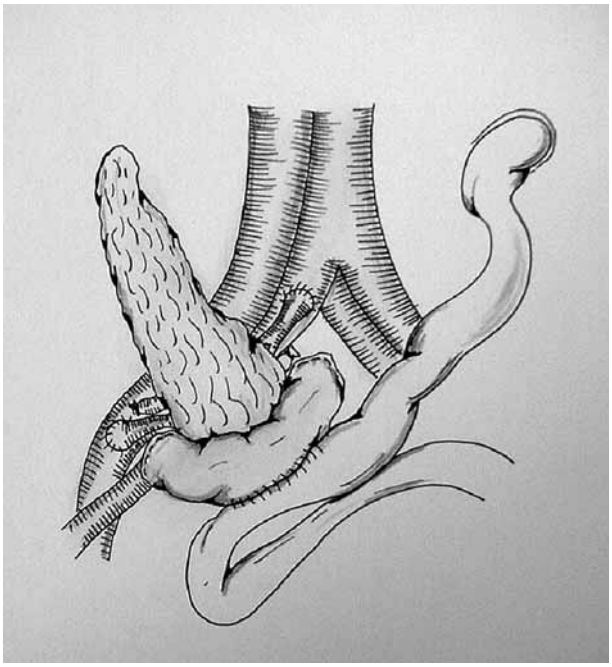


Fig. 1
a. graft arterial anatomy ; b. venous anastomosis, first era ; c. bladder drainage ; d. enteric drainage

Actuarial pancreas allograft survival in the first era was 80 and 74% respectively at 1 and 5 years post-transplant. Actuarial pancreas allograft survival in the second era was 89 and 84% respectively (Fig. 3). With exclusion of death with a functioning graft (n = 12), venous thrombosis remained the main cause of pancreas allograft loss (n = 5). Of note, no venous thrombosis was documented after change of the technique to the

Table II

Immunosuppression

Immunosuppressive regimen : protocol		
Induction :		FK506 : 0.1 mg/kg
		Mofetil : 1 g
		Simulect : 20 mg (day 1 + day 4)
		Solumedrol : 500 mg
Maintenance :		FK506 : 0.1 mg/kg -> target blood level 15-20 mg/ml
		Mofetil : 2 × 1 g
		Medrol : 16 mg
Immunosuppressive regimen : our patients		
Induction (n = 80)		
• No		5
• ATG	10 days	35
	4 days	17
	+ simulect	1
• Simulect		22
Maintenance (n = 80)		
• Cyclosporine		35
• Mofetil (study)		14
• FK506-MMF-steroids		29
• FK506-rapa-steroids		1
• MMF-rapa-steroids		1

Table III

Cause of patient death

Survival	
12 patients succumbed with functioning pancreas graft :	
• infarction or CVA	3
• CVA	3
• bronchopneumonia, sepsis	2
• bleeding (mycotic aneurysm)	1
• neurological	1
• breast cancer	1
• general status	1
3 of these non functioning kidney (chronic rejection)	
1 patient multi-organ failure after venous thrombosis and pulmonary emboli	
1 patient general status, functioning kidney, venous thrombosis pancreas	
1 patient dialysis	

lateralization of the venous anastomosis (2nd era > 1997). Other causes of allograft failure are documented in table IV.

Actuarial kidney allograft survival at 1 and 5 years posttransplant in the first era was 94 and 82% respectively. Actuarial kidney allograft survival at 1 and 5 years posttransplant in the second era was 93 and 84% respectively (Fig. 4). Causes of graft failure are included in table IV.

5. *Graft function*

Mean serum creatinine in the patients with functioning graft was 1.53 ± 0.64 mg/dl at 1 year, 1.75 ± 0.68 and 1.86 ± 0.87 respectively at 3 and 5 years follow-up.

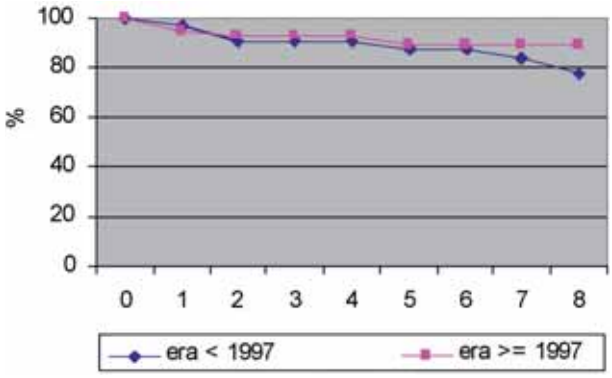


Fig. 2
Patient survival

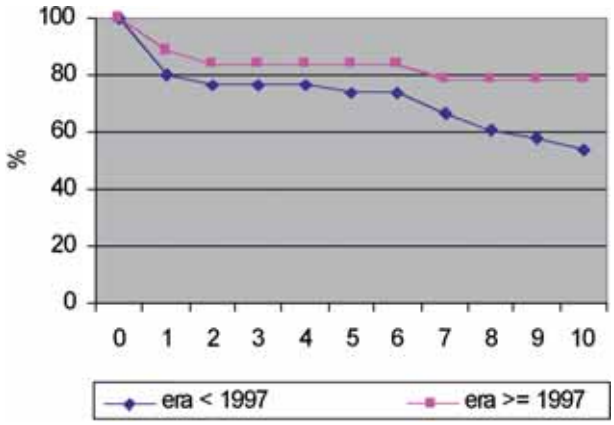


Fig. 3
Pancreas survival

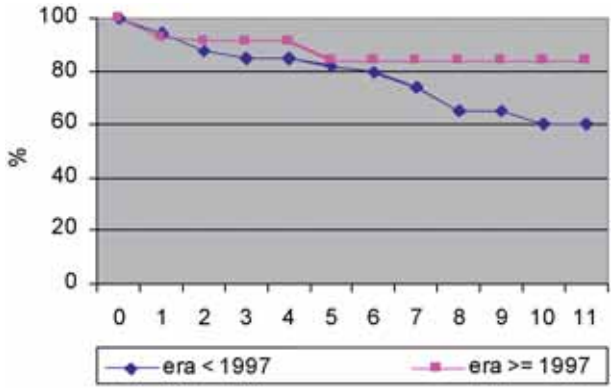


Fig. 4
Kidney survival

Measured creatinine clearance was 52.17 ± 17.85 mg/dl at 1 year, 49.61 ± 15.49 and 51.75 ± 23.19 mg/dl respectively at 3 and 5 years posttransplant.

In SPKTx patients with functioning pancreas graft at 1 year posttransplant, normoglycaemia is achieved. The

Table IV

Causes of allograft failure

Survival		
Pancreas allograft loss :		
• death with functioning graft	12	
• venous thrombosis	5 (first era)	
• chronic rejection	1	
• uncontrollable acute rejection	1	
• necrosis (non compliance)	1	
• pancreas transplant lymphoma	1	
• CMV, followed by bacterial infection	1	
Pancreatectomy in all except 1 (chronic rejection)		
Kidney allograft loss :		
• death with functioning graft		10
• multi-organ failure		1
• chronic rejection		4
• uncontrollable acute rejection		1
• chronic rejection, recurrent diabetic nephropathy (retransplantation)		1

pancreatic allograft functional studies at 1 year post-transplant showed a mean HbA1c of 5.1 ± 0.6% (versus 8.3% before combined transplantation), and a mean concentration of C-peptide of 1.1 nmol/l and 2.7 nmol/l respectively before and after stimulation with glucagon.

6. *Posttransplant surgical morbidity*

Mean hospital stay was 32.4 days (12-1) ; 58.1% stayed in hospital for less than 15 days ; 37.8% and 4.1% respectively for 15 to 30 days or longer.

Except pancreatectomy for vascular thrombosis (five patients) and reintervention for urologic complications (seven patients), early relaparotomy was performed in 6.3%. Indications were bleeding (n = 1 at the pancreatic tail and 1 because of mycotic aneurysm of the renal artery), small bowel volvulus (n = 1), deep infection (n = 1), exploration for oedema of the pancreatic head (n = 1).

Bleeding was present in 6.3% (treated with relaparotomy in patients as already mentioned and conservatively treated in 3 other cases (n = 2 wound, n = 1 at the hilum of the kidney).

12.5% of the patients developed wound problems : incisional hernia (n = 5), bleeding (n = 2), dehiscence (n = 2) and an abscess (n = 1).

Urologic complications inherent to the bladder drainage technique were : bladder- or duodenal segment leaks (13.3%) ; urethritis and urethral strictures with or without fistula (17.8%) ; recurrent haematuria (8.9%) ; urinary tract infections (80%) ; recurrent vulvitis and cystitis (8.9%) (table V). Enteric conversion (where the duodenocystostomy is broken down and an anastomosis side-to-side or with a Roux-en-Y small bowel loop between the duodenal segment and the small bowel is constructed) was performed in 6 of the 45 bladder-drained grafts. Urethral stricture may require dilatation or a Sachse urethrotomy ; first line treatment for a fistula is temporary suprapubic cystofix drainage.

Only 5.7% of patients with enteric drainage developed urologic problems (one hydrocoele, one urethrastenosis) and 20% suffered from urinary tract infections.

Prolonged postoperative lymphatic drainage was seen in nine patients and were treated conservatively in 8 and by a temporary drain in 1.

7. *Postoperative other morbidity*

Table VI gives an overview of diagnosis and treatment of rejection.

Bacterial infections were documented in 31.3%. Causes were osteomyelitis (n = 11), bronchopneumonia (n = 7), bronchitis (n = 6) and encephalitis (n = 1).

Twenty five percent of the patients developed an opportunistic or viral infection. Causes were cytomegalovirus (n = 8), herpes simplex or zoster (n = 6), polyomavirus (n = 3) and combination of cytomegalovirus and pneumocystis carinii (n = 2).

Allograft pancreatitis was present with 16 episodes in patients with functioning allograft (13 bladder drained, 3 enteric drained). It was usually successfully treated with temporary bladder drainage and total pancreatic rest including parenteral nutrition with additional Somatostatine®.

Two patients developed a pseudocyst, treated conservatively ; one patient underwent pancreatectomy because of necrosis (rejection) ; two patients were treated with drainage or conversion respectively because of infection and fistula formation.

Table V

Urologic complications

Bladder drainage (n = 45) ; 51.1% (n = 23)		
• leak	drain	1
	suture	2
	conversion	3
• urethra stenosis and fistula	cystofix	1
	cystofix and dilatation	1
	cystofix and Sachse urethrotomy	1
	perineostomy	1
• urethra fistula	cystofix	2
• urethra stenosis	dilatation	1
• vulvitis / cystitis	conversion	2
	conservative	2
• hydronephrosis	temporary pyelostomy	1

Table VI

Rejection

Rejection		
Diagnosis		
• acute	n = 1	26 (1 uncontrollable)
	n = 2	9
	> 2	1 (re-dialysis and loss of pancreatic function)
• chronic		3 (1 recurrent diabetic nephropathy, retransplantation)
First-line treatment with corticosteroids		
Additional treatment		
• OKT3		3
• Medrol-OKT3		3 (1 pancreatectomy and kidney transplantectomy)
• Medrol-ATG		1

Discussion

Significant changes in the medical and surgical approaches to SPKTx have resulted in dramatic beneficial effects on patient and graft survival (4, 6).

Our 5-year actuarial survival in SPKTx with 89%, 84% and 84% respectively for patient, pancreas and kidney compares favourably with data of the International Pancreas Transplant Registry and data of recent comparative studies between SPKTx and kidney alone transplantation (2, 3, 7).

A recently published single-center European institution study on long-term follow-up of 78 SPKTx described 5-year patient, pancreas and kidney survival of 81%, 73% and 67% respectively (8).

Vascular thrombosis is still the leading cause of non-immunologic pancreatic graft failure with a 6.3% occurrence in our series. There is a great variation in incidences reported in the literature from 1% to 19%. Seventy percent occurs within the first postoperative days (9-11). The intrinsically low microcirculatory flow through the pancreas is in part responsible but this phenomenon may also accompany pancreatitis or rejection. Older donors, donor death due to cardiovascular or cerebrovascular disease, segmental graft, inappropriate vascular supply, portal venous extension graft and graft pancreatitis are important risk factors for vascular pancreatic graft thrombosis.

In our series, five pancreata were lost due to venous thrombosis, all in the first era. This is the most important factor responsible for the difference in pancreas allograft survival between the two era (respectively 89 versus 80% at 1 year posttransplant). Porto-systemic venous anastomosis was performed between the graft portal vein and the native external iliac vein in the fist era (31 cases). In the second era, the graft portal vein was anastomosed to the common iliac vein *laterally* to the arterial vessels after thorough mobilization. This results in a more straight course of the venous circulation and prevents venous kinking due to the cross over of the portal vein over the external iliac artery in the previously used technique.

A strict control of the postoperative fluid balance by maintaining adequate intravascular volume and arterial pressure to assure good perfusion of the pancreatic allograft is also pivotal to prevent early graft thrombosis.

We recommend the subcutaneous use of low molecular weight heparin (dose depending on current

renal function). Controversy persists about efficacy of full-dose heparin or the use of platelet aggregation inhibitors (9, 10).

Although SPKTx compared with cadaveric kidney transplant alone is associated with better long-term patient survival, literature data describe a higher initial overall mortality risk mainly attributed to infection and the more aggressive nature of this surgical procedure (2, 3, 12).

With the modification of the venous vascular anastomosis and the subsequent elimination of reintervention for venous thrombosis, our early relaparatomy rate has dropped to only 6.3% which looks favourable compared to other series.

The use of postoperative systemic full heparinization results in a higher frequency of bleeding necessitating reintervention (9, 10). Similar to recent literature data, our anticoagulation policy with low molecular weight heparin during patient hospitalization lowers considerably this risk (8, 13).

From 1987 through 1995, most SPKTx were performed with bladder drainage by the duodenal segment technique. The advances in preservation, donor selection and immunosuppression, which place the duodenal segment at a lower risk for ischaemic or immunological injury, have rekindled the interest of surgeons for primary enteric drainage (14-18).

Urologic complications are specific to bladder drained pancreas transplants. The most frequent complications are bladder- or duodenal segment leaks, urethritis and urethral strictures, recurrent haematuria and urinary tract infections (14, 19). Urethral complications including urethritis, urethral disruption and strictures occurred in 23.3% of our patients. Reported frequency in the literature varies between 3% and 6%. Because urine in bladder drained pancreas transplants is alcaline due to the pancreatic bicarbonate excretion, pancreatic enzymes are activated and subsequently damage the mucosa of bladder and urethra. Most episodes of urethritis and urethral disruption in our patients healed conservatively with the sonographic guided placement of a temporary suprapubic bladder cystofix catheter (20). An urethral stricture may require additional dilatation, the placement of a stent or an internal urethrotomy. Although enteric conversion was only performed in 11.1% of our bladder drainage patients, some authors advise early enteric conversion (21, 22). The duodenocystostomy is broken down and an anastomosis side-to-side or with a Roux-en-Y small bowel loop between the duodenal segment and the small bowel is constructed.

The frequency of urinary tract infections in the bladder drainage patients is statistically significantly higher in SPKTx than in isolated kidney Tx with an occurrence of 80%. Reported occurrence in the literature varies between 10% and 62% (14, 20). The normal defences of the urinary bladder may be altered by the presence of pancreatic secretions (alcaline urine and mucosal damage), increasing the likelihood of infection. Incomplete bladder emptying (neuropathic bladder) in the diabetic patient may also play an important role.

Allograft pancreatitis is a specific problem in the SPKTx patient. Nearly all cases are bladder-drained exocrine drainage. It was always successfully treated with temporary bladder drainage and total pancreatic rest including parenteral nutrition with additional Somatostatine®. The frequency of this complication varies from 4.9% to 19% (11, 23). It results from some degree of ischaemia/reperfusion injury or from retrograde urinary backpressure (reflux pancreatitis) sometimes accentuated by inadequate bladder emptying in diabetic patients with a neurogenic bladder, or by urinary infection.

Although a heavier immunosuppressive regimen is used, the frequency of opportunistic and viral infections was acceptable. With the routine use of acyclovir or gancyclovir, the occurrence of CMV disease was only 12.5% in our SPKTx which is in contrast with literature data of 21% to 26% occurrence. However without the use of CMV prophylaxis frequency of infection may reach 50% (24, 25).

With the routine use of sulfamethoxazole/trimetoprim, the occurrence of pneumocystis carinii pneumonia in our SPKTx was 2.5% which is comparable with literature data.

Conclusions

With accumulated experience, adaptation and standardization of the surgical techniques, SPKTx has evolved into a safe transplantation procedure. Perioperative morbidity has become very low and results are excellent in terms of both patient (~95% 1-year survival) and graft survival (~90% 1-year survival). These results compare favourably with those reported by the International Pancreas Transplant Registry. In particular, enteric drainage has eliminated the urologic complications previously seen with the bladder drainage technique and has dramatically reduced the incidence of graft pancreatitis. Lateralization of the portal vein anastomosis has virtually eliminated the occurrence of early pancreatic graft thrombosis. The incidence of early relaparotomy has become extremely low. Excellent donor quality, meticulous donor *and* recipient surgery, and recipient management are all determinant in the success of SPKTx.

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