Advantages and Disadvantages of Urinary Tract Diversion in Clinical Pancreas Transplantation

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THE METHOD of duct management that is optimal for pancreatic (P) transplantation (Tx) continues to be a major controversy. An analysis of the *Pancreas Transplant Registry* shows no differences in results for the three major duct management techniques, polymer injection, enteric drainage, and urinary tract diversion (UTD). All techniques have advantages and disadvantages. Duct injection is safe but may lead to loss of the graft as a result of severe fibrosis. Enteric drainage is the most physiologic method but may lead to intra-abdominal infection. Neither duct injection nor enteric drainage allows for permanent monitoring of exocrine function.[1] These studies may be important, as the experimental studies indicate early involvement of the exocrine followed by the endocrine component in the rejection process.[2,3] The methods of UTD are to anastomose the pancreatic duct of segmental grafts or the duodenum of whole pancreas graft to the renal pelvis, the ureter, or directly to the bladder.[4,5,6]

We describe herein the advantages and disadvantages using the UTD. We report our observations of the physiologic consequences of diversion of exocrine secretions into the urinary tract focusing their relationship to the rejection process and on the measurement of the urinary C-peptide.

PATIENTS AND METHODS

Our total experience comprises 12 combined cadaveric renal (K) and PTx with both of the organs provided by the same donor and three patients nonuremic, nonkidney transplant, diabetic patients with mild renal disease. Their age range was 29 to 54 years. In four patients a segmental graft and a pancreaticopyelostomy (renal pelvis) were performed. In five patients, the whole pancreas without the duodenum but preserving 2 cm of duodenal wall surrounding the ampulla of Vater was anastomosed to the ureter. In six patients, the whole pancreas was anastomosed directly to the bladder. In 5 patients, immunosuppression consisted of azathioprine and prednisone, and in 10 patients, triple immunosuppressive protocol that included cyclosporine, prednisone, and azathioprine.

RESULTS

Three patients failed immediately after the operation for venous thrombosis. Two patients died, one 72 hours after Tx for miocardial infarction with both K plus P functioning, and another, 2 weeks after Tx for septic shock after acute pancreatitis of the graft. In one patient, the pancreas was removed after 6 weeks with good endocrine and exocrine graft functioning; an urinary obstruction led to a disruption and leakage of the pancreaticocystostomy anastomoses.

Rejection was the leading cause of failure in seven patients. In six patients, a significant decrease in urinary amylase had a high correlation with rejection episodes. In all but one patient, rejection was treated with high doses of steroids and eventually had graft failure. In one patient with simultaneous K plus PTx, no attempt was made to reverse rejection 7 months after Tx despite a significant drop of urinary amylase (UA) and marked elevations of serum amylase. This decision was based on the good renal function and the poor general health of the patient. This patient is still alive and well. One patient had an episode of rejection of kidney (elevation of serum creatinine) and pancreas (decrease of UA) 2 weeks after simultaneous Tx. Three months later, however, hyperglycemia occurred with concomitant elevated levels of UA and normal serum

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Table 1. Patient E. R., 32-Yr-Old (Kidney and Pancreas Transplantation)

	Whole Organ Pancreatico cystostomy			
	Weeks After Tx	Glucose (mg/dl)	Amylase (IU/day)	Creatinine (mg/dL)
Before rejection	1	105	252,207	1,4
Rejection	4	78	84,614	2,7
Graft stabilization	5-12	93	284,080 ± 62000	1,1
Rejection	13	>400*	121,342	1,3†

Significant drop of UA at the time of kidney (elevation of serum creatinine) rejection. After 12 weeks with good renal and pancreas, functioning had an increase of serum glucose with elevated level of urine amylase. A marked decrease in UA was noted only as a late manifestation of irreversible rejection.

*Resume insulin treatment

†Currently functioning 9 months after Tx

creatinine initiating rejection treatment. A marked decrease in urinary amylase levels was noted only as a late manifestation of irreversible rejection (Table 1).

Two patients are currently with both K and P functioning for 50 and 18 months respectively. The patient with the graft surviving for more than 4 years continues to have elevated levels of UA. This graft shows patency of the anastomoses and no deterioration with time of the exocrine and endocrine tissue (Table 2).

Three patients had episodes of metabolic acidoses, and it was necessary to provide adequate replacement by oral bicarbonate alone during periods of renal dysfunction from renal allograft rejection. Metabolic acidosis occurred as early as 1 week and as late as 18 months post-Tx. All patients during episodes of renal dysfunction were normoglycemic and with elevated levels of UA and serum bicarbonate ranged between 15,4 and 20,46 mEq/L. One patient (No 1) has chronic metabolic acidosis with both K and P functioning for more than 18 months and still necessitates oral bicarbonate 15 g daily (Table 3).

Urinary C-peptide (U C-peptide) was measured in three patients showing in one patient a mean of 3.1 ± 2.2 μg/d ranging between 1-10.2 μg/d, another a mean of 19 ± 16 μg/d ranging between 4.2-31 μg/mL, and the third patient 2.15 ± 2.7 μg/d ranging between 0.45-2.9 μg/d. These low values, below normal for individuals (42.1 ± 16.3 μg/d), were in contrast with high levels of mean plasmatic C-peptide, 9.8 ± 5 ng/ml, 4.1 ± 1.7 ng/mL, 9.2 ± 5.1 ng/mL, respectively, in each

Table 2. Patient C.C., Female 30-Yr-Old (Kidney and Pancreas Transplantation)

	Pancreatico pyelostomy		
	Weeks after Tx.	Urinary Amylase (IU/24 h)	Urinary Lipase (IU/24 h)
Before rejection	1	3375 ± 1634	—
Rejection	1	973	—
After rejection	2-3	3880 ± 2723	—
	Years after Tx.		
	1	76817 ± 10900	—
	2	86665 ± 20927	137000 ± 17400
	3	100018 ± 19645	80000 ± 15620
	4*	97106 ± 20114	105644 ± 21200

Patient with simultaneous K plus P Tx (pancreaticopyelostomy and portal venous drainage). Significant drop of UA at the time of rejection. Elevated levels of UA throughout the 4 years after Tx as well as urine lipase in the last 3 years. The preservation of the normal anatomic and physiologic relationship between acinar and islet cell component is demonstrated.

*Kidney currently functioning, creatinine ranging 1-1,4 mg/dL

Table 3. Metabolic Profile of Pancreatic Transplants Recipients with Urinary Tract Diversion

	Patients		
	1	2	3
Period of renal dysfunction (Weeks after Tx)	5-20	2-6	1-4
Mean s. Creatinine (mg/dL)	2,55	1,98	1,73
Mean HCO_3 (mEq/L)	15,4	16,43	20,46
Mean pH	7,35	7,20	7,28
Mean s. Glucose (mg/dL)	70 ± 15	85 ± 11	98 ± 4
Mean U. Amylase (IU/day)	293328 ± 120412	139313 ± 64000	199750 ± 78310
Oral bicarbonate (daily)	9-21 g	3-9 g	3-9 g

All patients during episodes of renal dysfunction were normoglycemic and with elevated level of UA resulting in clinical metabolic acidosis necessitating oral bicarbonate.

patient. In all patients, UA levels were significantly elevated (Table 4). These results questioned the validity of the measurement of the U. C-peptide as a reliable method of assessing the beta cell secretion in patients with good renal function.[7] In one additional patient with a simultaneous K + PTx and whole organ pancreaticocystostomy technique, we tested the use of the measurement of the U. C-peptide keeping the urine out from the bladder through a nephrostomy catheter for 2 weeks after Tx. All the exocrine pancreatic drainage was collected daily through an urethral catheter, and amylase was studied. A gradual increase of this enzyme was observed (2000-38000 IU/d) reaching higher values 1 week after the operation. Normal plasma glucose was obtained immediately after Tx and C-peptide levels were persistently high, 4,2-5,6 ng/mL throughout the following days. At the same time U. C-peptide levels remained high 114-132 μg/d. These values dropped abruptly (4 μg/d), however, when renal catheter was removed. These results suggest that the C-peptide molecule was destroyed by the pancreatic enzymes (Fig 1).

DISCUSSION

Rejection and technical complications are the leading causes of failure in clinical PTx. UTD provides an advantage for monitoring graft function and treating rejection.[8,9] Animal experiments and clinical experience have shown that an increase in plasma glucose is a late indication of pancreatic rejection while a decline in UA in UTD grafts is an early indicator of rejection.[2,3,10] However, this has not been a constant finding in our experience. Although one patient had a significant drop of UA at the time of kidney rejection, a second episode of pancreas rejection with hyperglycemia and normal renal function was associated with elevated levels of UA; a marked decrease of UA was noted only as a late manifestation of irreversible rejection. The preservation of the normal anatomic and physiologic relationship between acinar and islet cell component is clearly demonstrated in

Table 4. Effect of Urinary Tract Diversion on U. C-peptide

	Patients		
1 mo after Pancreas Transplantation	AM	JAC	RR
Mean urinary C-peptide (NV:38 ± 16 μg/d)	3,1 ± 2,2	19 ± 16	2,15 ± 2,7
Mean plasmatic C-peptide (NV:0,5-2,1 ng/mL)	9,8 ± 5,0	4,1 ± 1,7	9,2 ± 5,1
Range urine amylase (IU/d)	1480-87766	2800-35041	1800-19120

Low levels of urinary C-peptide despite elevated values of plasma C-peptide. In all patients UA was significantly elevated. NV, normal value.

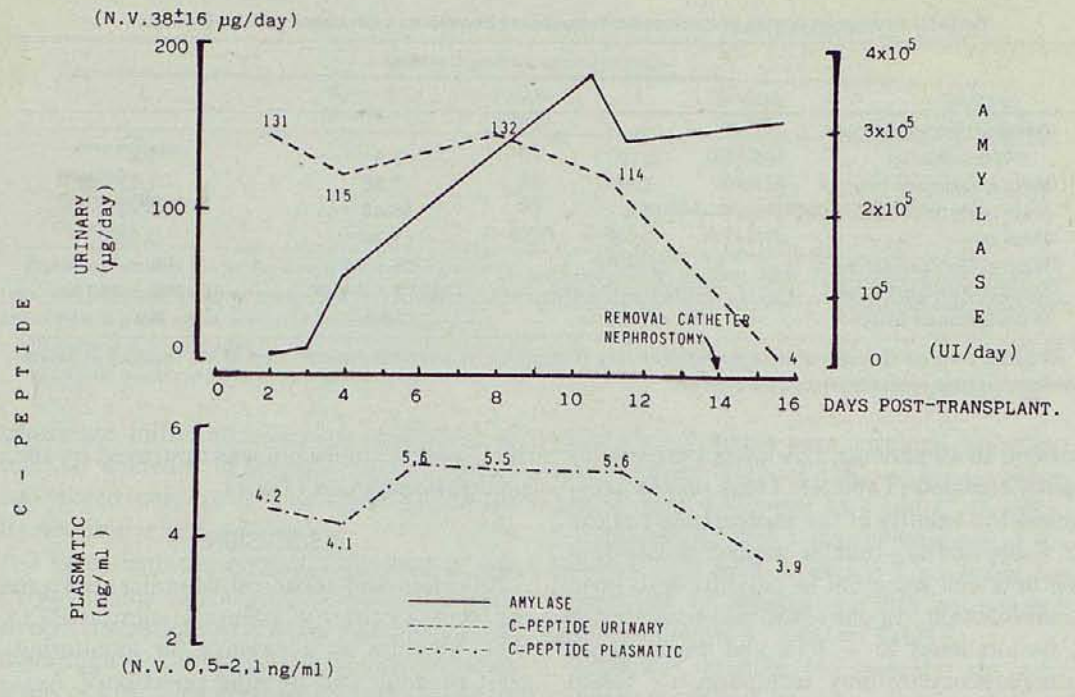

Fig 1. Patient with simultaneous K plus PTx. During 14 days all urine collected through a nephrostomy catheter. Exocrine pancreatic secretion collected through an urethral catheter. A gradual increase of UA was noted after Tx. Normal serum glucose and elevated levels of plasmatic C-peptide. Urinary C-peptide levels remained high after Tx, but dropped abruptly when renal catheter was removed.

one patient with a segmental graft drained into the renal and portal venous drainage, currently functioning for more than 4 years.

The major disadvantage of UTD is the obligatory loss of bicarbonate from the pancreas graft resulting in a metabolic acidosis[11,12] particularly during periods of renal dysfunction from allograft rejection as we have seen in three of our patients. In patients with UTD, the measurements of the U. C-peptide excretion is an unreliable method of assessing the beta-cell secretion. The significant decrease of U. C-peptide levels after mixture of urine with the pancreatic exocrine secretions, coexisting with elevated plasma levels, strongly suggests that the C-peptide molecule was destroyed by the pancreatic proteolitic enzymes.

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