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Simultaneous Pancreas-Kidney and Pancreas Transplantation

BRYAN N. BECKER,* JON S. ODORICO,† YOLANDA T. BECKER,† MARILYN GROSHEK,† CATHY WERWINSKI,† JOHN D. PIRSCH,† and HANS W. SOLLINGER†

**Division of Nephrology, Department of Medicine, and †Division of Transplantation, Department of Surgery, University of Wisconsin, Madison, Wisconsin.*

The discovery of insulin in 1922 changed the treatment of type 1 diabetes mellitus (DM) forever. Insulin was the first effective therapy for type 1 DM; however, its success engendered a terrible paradox for patients with this disease. The use of insulin transformed type 1 DM from a rapidly fatal condition to a chronic incurable illness, revealing the long-term complications associated with DM, *e.g.*, nephropathy, vasculopathy, retinopathy, and neuropathy, and the terrible toll that they take throughout a lifetime.

DM now affects approximately 20 million individuals in the United States, with at least 2 million individuals having classic type 1 DM (1). Hyperglycemia, alone or in concert with hypertension, is the primary factor influencing the development of major diabetic complications (2,3). Therefore, correcting hyperglycemia is an obvious strategy for altering the course of DM and its complications. The Diabetes Control and Complications Trial (4) demonstrated that glycemic control could limit the rate of progression of complications in type 1 DM. However, the best available method for achieving a steady euglycemic state among individuals with type 1 DM is whole-pancreas transplantation.

The goals of pancreas transplantation have developed beyond simply restoring normoglycemia for a period of time and improving the quality of life (QOL) (5). Pancreas transplantation, as simultaneous pancreas-kidney (SPK) transplantation or pancreas transplantation alone (PTA), is now a functional and effective therapy that can reverse metabolic abnormalities (6) and prevent or minimize many of the secondary complications of DM (7). Perhaps even more significantly, pancreas transplantation now seems to be a therapy that can improve survival rates in the setting of type 1 DM (8).

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Correspondence to Dr. Bryan N. Becker, University of Wisconsin, Nephrology B3063, 2500 Overlook Terrace, Madison, WI 53705. Phone: 608-263-5925; Fax: 608-263-0568; E-mail: bnb@medicine.wisc.edu

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Candidates for Pancreas Transplants

Pancreas transplantation was first performed in 1966 (9). Since then, nearly 14,000 pancreas transplants have been reported to the International Pancreas Transplant Registry (10). C-peptide-deficient, insulin-dependent patients with type 1 DM and significant nephropathy or end-stage renal disease (ESRD) are potential candidates for SPK transplantation if they are <55 yr of age. Ideal patients for PTA are individuals with type 1 DM, low cardiac risk, and relatively mild and potentially reversible end-organ disease (Table 1) (11). The majority of pancreas transplants performed in the United States are for C-peptide-deficient individuals with DM. However, some insulin-dependent patients with normal C-peptide levels can achieve good glycemic control after pancreas transplants (12). This finding may reflect a greater native pancreatic β-cell reserve than expected, a greater transplanted β-cell load, or the problematic nature of C-peptide measurements as markers of type 1 DM, especially among patients with renal disease (13).

Significant cardiovascular disease is a contraindication to pancreas transplantation. A history of coronary revascularization is a less significant contraindication than in the past. Nevertheless, coronary event rates remain greater among pancreas transplant recipients who have undergone coronary revascularization (11% at 1 yr and 29% at 3 yr after transplantation), compared with individuals without pretransplantation coronary artery disease (2% at 1 yr and 8% at 3 yr) (14). Therefore, individuals with significant coronary artery disease are often preferentially referred for kidney transplantation alone (KTA), although they can subsequently receive a PTA after the kidney transplant (PAK).

Severe peripheral vascular disease is another relative contraindication to SPK transplantation and PTA. Although patients with DM-related ESRD can still benefit from SPK transplants, they are unlikely to derive improved peripheral vascular function, given our present understanding of post-SPK transplantation complications and disease (15). Moreover, iliac atherosclerosis can complicate the technical procedure. Other relative contraindications to pancreas transplantation include obesity, substance abuse, poorly controlled psychiatric illnesses, noncompliance, and any recent malignancy (11). Ultimately, the principal consideration in the selection of candi-

Table 1. Clinical eligibility criteria for potential SPK transplant and PTA recipients[a]

Age <55 yr
Low C-peptide levels
Minimal cardiovascular risk[b]
Absence of amputations secondary to DM-related peripheral vascular disease
History of adherence to medical recommendations and therapies
Ability to understand the procedure
Apparent willingness to subscribe to posttransplantation guidelines and management
Body mass index of <32
Presence of two or more potential end-organ complications related to type 1 DM[c]

[a] Adapted from reference 11. SPK, simultaneous pancreas-kidney; PTA, pancreas transplantation alone.

[b] Defined as a negative thallium stress test and/or absent or mild coronary artery disease.

[c] In the absence of chronic renal failure or end-stage renal disease secondary to type 1 diabetes mellitus (DM), this defines eligibility for PTA.

dates for pancreas transplantation is the balance between cardiovascular risk and the benefits of glucose homeostasis with respect to QOL, end-organ disease, and mortality rates.

Options Available for Potential Pancreas Transplant Recipients

SPK transplantation should be considered the primary transplant option for patients with type 1 DM who are acceptable candidates but for whom a suitable, HLA-identical, living donor is not available (Figure 1). Young diabetic patients with suitable, HLA-identical, living donors should also consider HLA-identical kidney transplantation. This option offers superior long-term renal graft function results, with less immunosuppression than required for SPK transplantation. Moreover, this procedure does not disqualify patients from PTA at a later time or concurrent with the kidney transplantation (16). An optimal HLA-identical donor should lack islet cell antibodies (a risk factor for type 1 DM) and should be provided with information about the risks of developing type 1 DM in the future. It should be noted also that the long-term renal graft function for SPK transplant recipients is comparable to that for haplotype-identical or living unrelated donor kidney transplant recipients (17).

Individuals who undergo HLA-identical kidney transplantation and then PAK transplantation are part of an increasing group of PTA recipients throughout the world (18). Such individuals now account for 9% (PAK transplantation) and 4% (PTA) of all pancreas transplants in the United States. The indications for PAK transplantation are relatively broad, because these patients are already undergoing life-long immunosuppression. However, patients with stable kidney transplant function (creatinine clearance of ≥50 ml/min and the absence of significant proteinuria) should be considered for PAK transplantation. Patients with marginal kidney transplant function are not candidates, because the intensified calcineurin inhibitor therapy after surgery can precipitate renal failure. Such individuals should be monitored carefully and considered for preemptive kidney retransplantation or SPK transplantation as their renal function declines further.

The presence of two or more diabetic complications that have not yet progressed to end-organ failure defines the eligibility criteria for PTA. These complications include early nephropathy, with microalbuminuria but preserved native renal function (normal serum creatinine concentrations and creatinine clearance values of ≥80 ml/min), and labile glycemic control, with recurrent hypoglycemia or hypoglycemic unawareness.

Finally, issues of access and reimbursement are important in pancreas transplantation. Pancreas transplantation needs to be offered to all potential candidates. Isaacs *et al.* (19) documented striking racial disparities in access to SPK transplantation in the United States, with Caucasian individuals receiving 92% of all SPK transplants. Those authors attributed these differences to differences in employment status, the prevalence of private insurance among certain racial and ethnic groups in the United States, and general health care. Their data supported the recent change in the Medicare policy pertaining to SPK transplantation. Medicare coverage was approved, as of July 1999, for clinically indicated pancreas transplantation in the SPK and PAK transplantation settings.

Surgery

The critical aspects of the transplant operation are donor selection and preparation of the pancreaticoduodenal allograft. Optimal pancreas donors are young (age, 4 to 55 yr), nondiabetic, nonobese, and without significant aortoiliac atherosclerotic disease. Pancreata from obese and/or older donors are associated with an increased risk of postoperative intra-abdominal infections and poor posttransplantation glycemic control (20). Most transplant surgeons also consider "fibrotic or fatty" pancreata to represent higher risks. However, the effects of these characteristics on outcomes have not been formally evaluated. Preoperative isolated donor hyperglycemia or hyperamylasemia is actually not a contraindication to the use of the pancreas for transplantation. Ultimately, the most important determinant of suitability is the intraoperative assessment of organ quality by an experienced transplant surgeon.

During cadaveric donor operations at our center, the donor pancreas, duodenum, and spleen are perfused *in situ* with cold University of Wisconsin solution and are collected *en bloc* with the liver. The pancreaticoduodenal graft is then separated from the liver graft at 4°C. The technical aspects of the recipient procedure are largely the same whether SPK transplantation, PTA, or PAK transplantation is being performed. The native pancreas is not removed, because it may still provide some digestive function. The pancreaticoduodenal allograft is transplanted to an ectopic location, usually the right iliac fossa. The kidney allograft is transplanted ectopically to the contralateral iliac fossa. Solitary pancreaticoduodenal allografts can be implanted into either iliac fossa, although the right side is used more frequently. In all other respects, the operative sequence

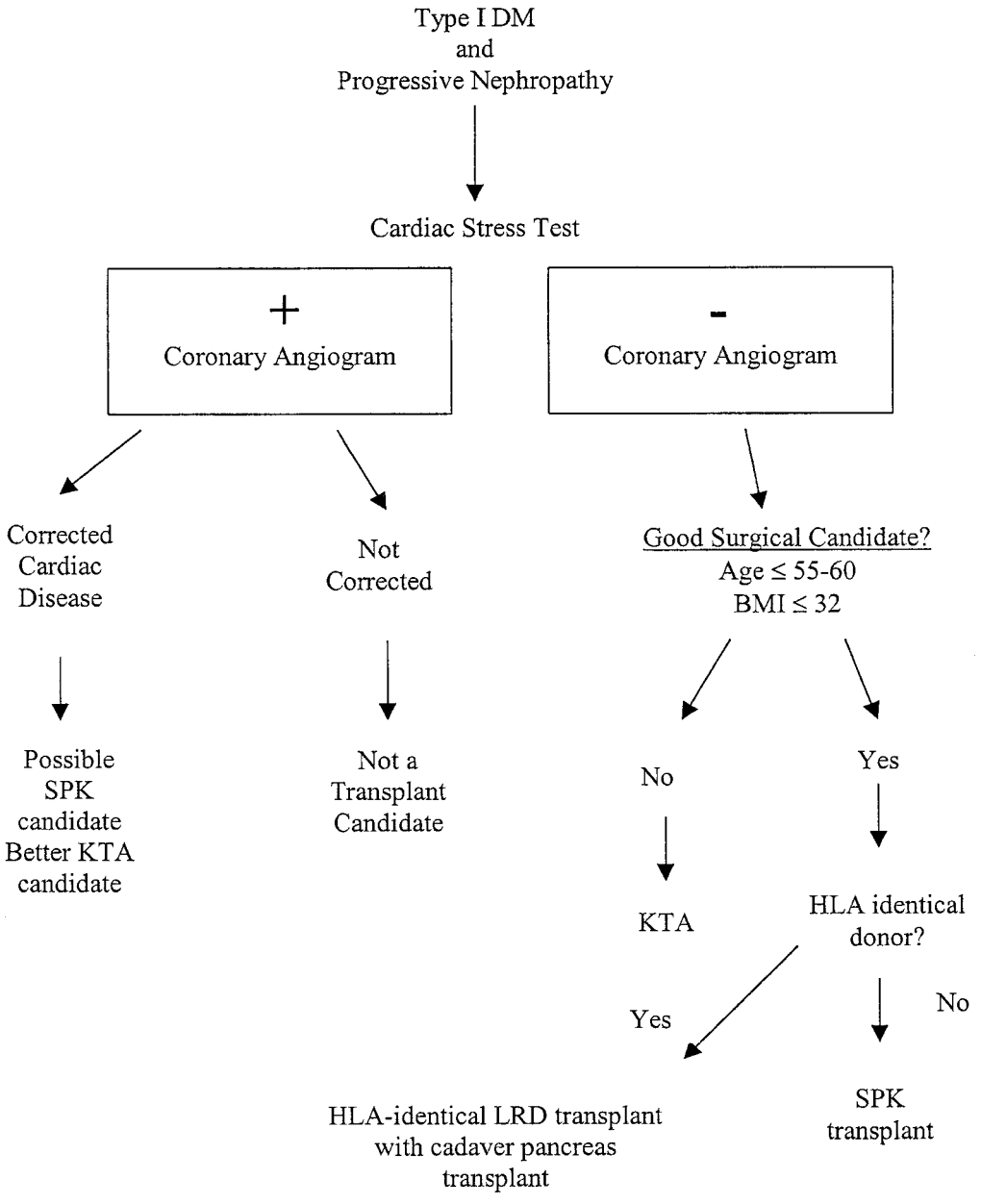

Figure 1. Options for potential simultaneous pancreas-kidney (SPK) transplant recipients. DM, diabetes mellitus; BMI, body mass index; KTA, kidney transplantation alone; LRD, living related donor.

for PTA duplicates the combined procedure. Intraperitoneal placement of the pancreatic allograft is important. This technique is associated with fewer peripancreatic fluid collections and wound complications. Previous peritoneal dialysis increases the risk of postoperative intra-abdominal fluid collections related to lymphatic or pancreatic secretions.

Systemic venous drainage is obtained by anastomosing the donor graft portal vein to the recipient iliac vein or inferior vena cava. Portal venous drainage is an alternative approach in which the portal vein of the allograft is anastomosed to the superior mesenteric vein of the recipient. This technique results in drainage of released insulin into the portal venous blood flow.

There is debate regarding whether this is the most physiologic drainage technique. Systemic venous drainage can result in peripheral hyperinsulinemia. However, mild peripheral hyperinsulinemia is present among the vast majority of all transplant recipients. Systemic insulin release does lead to greater peripheral hyperinsulinemia, compared with portal venous drainage (21); however, the long-term results of the two techniques are comparable. Ultimately, the method of venous drainage may be dictated by the anatomic considerations for each patient.

PTA recipients, by definition, have good renal function and thus lack the platelet dysfunction so common in ESRD. This may explain the increased risk of graft thrombosis (venous or

arterial) in this population (10%), compared with SPK transplant recipients (6.4%) (22). Intra-arterial or systemic heparin administration is often performed perioperatively, with subsequent antiplatelet therapy (*e.g.*, aspirin or dipyridamole), to decrease the likelihood of graft thrombosis.

Drainage of Pancreatic Exocrine Secretions: Bladder *versus* Enteric Drainage

A variety of techniques to manage pancreatic exocrine secretions, including duct occlusion, open drainage into the peritoneal cavity, anastomosis of the pancreatic duct to the ureter or bladder, and creation of a duodenal button for anastomosis to the urinary tract, have been proposed throughout the years (23). All of these techniques have been abandoned. Currently, bladder drainage (BD) of pancreatic exocrine secretions (Figure 2A) or drainage into the small intestine [enteric drainage (ED)] (Figure 2B) are the most commonly used techniques (22). The donor duodenum is anastomosed to the dome of the recipient bladder for BD, with exocrine secretions being diverted into the urinary tract. This technique, although safe and well tolerated, is associated with intravascular volume depletion, metabolic acidosis, reflux pancreatitis, and urinary tract complications, including hematuria, urethritis, urethral strictures, urethral disruption, and recurrent urinary tract infections (24). ED, in which the donor duodenal segment is anastomosed to the proximal to middle jejunum, might be more physiologic. ED is associated with significantly fewer urologic and metabolic complications, as well as fewer urinary tract infections and far fewer episodes of volume depletion, compared with BD (Table 2) (25). However, ED is associated with a significantly greater incidence of gastrointestinal bleeding, compared with BD (25).

BD is advantageous in certain instances, such as PTA, because it allows monitoring of urinary amylase levels as an indicator of rejection. Indeed, BD may be more important in this setting than in SPK transplantation. However, serial serum amylase and lipase determinations, combined with clinically indicated allograft biopsies, are also effective for rejection surveillance.

Symptomatic diabetic enteropathy, chronic constipation, or intraoperative exposure to prosthetic material are all relative contraindications to ED. Various genitourinary conditions, *e.g.*, neurogenic bladder, urethral strictures, or complex urinary tract abnormalities, are all relative contraindications to BD. Overall, ED is gaining popularity. In fact, United Network for Organ Sharing/International Pancreas Transplant Registry data demonstrate that an increasing number of centers are using ED (26). Because the long-term graft survival rates, thrombosis rates, and primary nonfunction rates are equivalent for the two techniques, the choice of drainage procedure remains an individualized surgical decision.

Rejection, Immunosuppression, and Organ-Specific Outcomes

The obvious goal of any transplant procedure is long-term graft survival. Until recently, the success of PTA or SPK transplantation was limited in part by early pancreatic graft thrombosis (3 to 12%) within the first yr. Studies have also

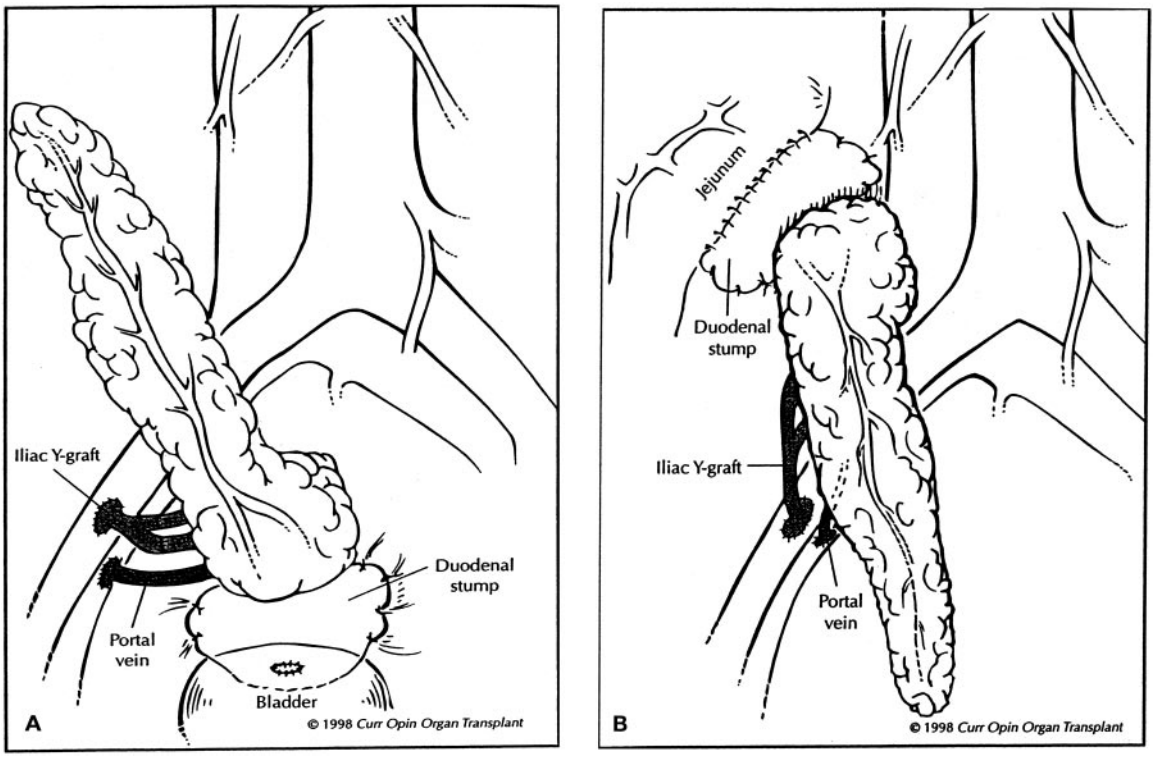

Figure 2. (A) Pancreas transplant with bladder drainage. (B) Pancreas transplant with enteric drainage. Reproduced with permission from Becker YT, Collins BH, Sollinger HW: Technical complications of pancreas transplantation. *Curr Opin Organ Transplant* 3: 253–257, 1998.

Table 2. Comparison of complications related to drainage technique[a]

Complication	Rate (%)		*P*
	ED	BD	
UTI	16	67	<0.0001
Pancreatic enzyme leak	5	18	0.05
bicarbonate replacement	16	65	0.001
mean dose (g/d)	3.8	8.8	0.0004
Urologic complications[b]	0	20	NS
Intestinal bleeding[c]	3.6	0	NS
Surgical conversion of drainage route	0	Up to 25	<0.001
Abdominal infection	12.1	16.4	NS
Pancreatitis	7.3	3.6	NS

[a] Adapted from reference 24. ED, enteric drainage; BD, bladder drainage; UTI, urinary tract infection.
[b] Urethritis, uretheral disruption or digestion, and hematuria.
[c] Putative source is enteric anastomosis.

suggested that SPK transplant recipients experience renal graft rejection more frequently than do KTA recipients (27,28) and that renal graft rejection may be more frequently confined to the tubulointerstitium *versus* the vascular compartment in SPK transplantation renal grafts (29). Interestingly, renal graft rejection may be two to three times more frequent than pancreatic graft rejection among SPK transplant recipients. However, it would be a mistake to discount pancreatic graft rejection, because this remains the single most significant cause of pancreatic graft loss (30).

The early diagnosis of pancreatic graft rejection is a clinical challenge. Renal graft rejection usually precedes or parallels pancreatic graft rejection after SPK transplantation. Pancreas rejection is subtle, with nonspecific findings such as fever, abdominal pain, allograft tenderness, and accompanying biochemical changes (*e.g.*, hyperamylasemia or increased serum creatinine levels) (31). Urinary amylase levels may decrease in BD pancreata, with concomitant changes in urinary cytologic features (32). There may even be rejection-induced changes in blood flow to the pancreatic allograft, with arteriolar irregularities, graft hypoperfusion, swelling, and diminished visualization of the pancreatic tail (31). Other tests that have been used to diagnose pancreas transplant rejection include ^{99m}Tc-diethylenetriaminepentaacetic acid scintigraphy, uptake of indium-labeled platelets, decreases in urinary insulin and/or C-peptide levels, and changes in human anodal trypsinogen or pancreas-specific protein levels (31). However, all of these noninvasive tests have significant limitations, leaving histopathologic examination as the standard for the diagnosis of rejection after pancreas transplantation.

Tissue samples for the diagnosis of pancreatic allograft rejection can now be routinely obtained by using percutaneous needle biopsy techniques. Bartlett and colleagues (33) assembled an array of pancreas transplant biopsies, along with pancreatic tissue exhibiting other disease processes, and described a set of vascular, septal, and acinar inflammatory characteristic criteria that defined pancreatic graft rejection (Table 3). Their grading scheme demonstrated a significant correlation with graft loss (0% for grades 0 and I, 11.5% for grade II, 17.3% for grade III, 37.5% for grade IV, and 100% for grade V), with the number of grafts lost because of purely immunologic causes increasing significantly with rejection beyond grade I.

There is little additional immunologic risk in receiving a cadaveric pancreas transplant with a kidney transplant (34). Indeed, the entrapment hypothesis (35,36) suggests that higher rates of blood flow to the kidney divert immunocompetent cells away from the pancreatic allograft, lessening the likelihood of

Table 3. Classification of pancreas allograft rejection[a]

Grade	Features
0	Normal
I	Inflammation of undetermined significance, with septal mononuclear infiltrates and the absence of venous or acinar involvement
II	Minimal rejection, with septal inflammation and venous endotheliitis (lymphocytes attached to the endothelium, with damage and elevation of the endothelium from the basement membrane); in the absence of venous endotheliitis, at least three of the following features also define grade II rejection: (*1*) septal inflammatory infiltrates with a mixed lymphocyte appearance (large "activated" and small lymphocytes), (*2*) eosinophils, (*3*) acinar inflammation in up to two foci (a collection of at least 10 mononuclear cells), or (*4*) ductal inflammation
III	Mild rejection, with septal inflammation consisting of a mixed lymphocyte population and acinar inflammation in at least three foci and with eosinophils, venous endotheliitis, ductal inflammation, and acinar single-cell injury as a byproduct of sampling error; the latter is present as cellular apoptosis or necrosis
IV	Moderate rejection, with arterial endotheliitis and/or necrotizing vasculitis, usually with features of grade III rejection also
V	Severe rejection, with extensive acinar lymphoid or mixed inflammatory infiltrates, with multicellular foci or confluent acinar necrosis

[a] Adapted from reference 33.

graft rejection. Alternatively, the presence of two allografts may "dilute" the number of immunocompetent cells that can affect a graft during a rejection episode, minimizing the extent of any immunologic response in the setting of SPK transplantation (37). Conversely, renal graft rejection may lead to loss of the renal allograft despite normal pancreatic graft function. The risk factors for graft loss after SPK transplantation are increasing donor age (*i.e.*, >45 yr), recipient age of >45 yr, and retransplantation (26). Interestingly, cold ischemia time (if <30 h), degree of HLA mismatch, choice of exocrine drainage procedure, and use of anti-T cell antibody therapy do not strongly affect outcomes (26).

The increases in graft function rates for PTA are more dramatic than those for SPK transplantation. The United Network for Organ Sharing/International Pancreas Transplant Registry now reports 1-yr pancreatic graft function rates of 76% for PAK transplantation and 72% for PTA (26). These rates represent marked improvements over the 20 to 50% 1-yr graft survival rates for such transplants in the era before University of Wisconsin solution and cyclosporine A (CsA). Several centers have reported even better results, *i.e.*, 85 to 90% 1-yr graft function rates (38).

Modern immunosuppression after pancreas transplantation generally includes anti-T cell antibody induction therapy in conjunction with a tacrolimus (TAC)/mycophenolate mofetil (MMF)-based regimen. SPK transplant recipients treated with TAC and MMF experienced 1-yr acute rejection rates of 22% for kidney grafts and 0 to 3% for pancreatic grafts, compared with 77 to 86% and 31 to 51% for kidney and pancreas, respectively, among patients treated with CsA and azathioprine (39). Patients treated with CsA and MMF experienced rejection rates slightly greater than those for TAC/MMF-treated patients (34% for kidney grafts and 5 to 10% for pancreatic grafts) (39). The current 1-yr graft function rates for pancreas (83%) and kidney (90%) reflect these remarkable improvements in decreasing the rate of rejection (26).

Benefits of Pancreas Transplantation

Survival Rates

Early studies suggested that the morbidity and mortality rates associated with SPK transplantation offset any potential survival advantage. In the middle 1990s, there was gradual reassessment of the effectiveness of SPK transplantation, with Douzdjian *et al.* (40) highlighting the improved 5-yr survival rates for SPK transplant recipients, compared with diabetic KTA recipients. Recently, the group at the University of Wisconsin demonstrated a similarly significant improvement after SPK transplantation with a different measure of survival, *i.e.*, the observed/expected survival ratio (27). These studies have been criticized for the lack of a true control population and selection biases that could affect SPK and KTA recipients. Even the well controlled study reported by Tyden *et al.* (41), which noted a reduction in 10-yr mortality rates after SPK transplantation, is susceptible to this criticism. Therefore, the data reported by Smets *et al.* (8) are of great significance. That group analyzed 415 patients with type 1 DM for whom renal replacement therapy was initiated in the Netherlands between 1985 and 1996. In one area, SPK transplantation was offered to patients. In another region, KTA was the transplant modality. SPK transplantation was associated with a hazard ratio for death of 0.53 (95% confidence interval, 0.36 to 0.77; $P < 0.0001$) when all eligible individuals with ESRD were evaluated. This hazard ratio decreased to 0.4 (95% confidence interval, 0.20 to 0.77; $P = 0.008$) when only transplant recipients were evaluated. Therefore, SPK transplantation seems to be a therapy that can reduce mortality rates among individuals with type 1 DM and ESRD.

Quality of Life

Pancreas transplantation counteracts many of the difficult aspects of type 1 DM, including hypoglycemic unawareness, metabolic derangements, fluctuating glycemic control, insulin dependence, glucose monitoring, and dietary restrictions. Therefore, it could be anticipated that pancreas transplantation would significantly improve the QOL for individuals with type 1 DM. The overwhelming majority of QOL studies that examined pancreas transplantation assessed SPK transplant recipients. Interestingly, researchers observed only a few areas in which QOL scores for SPK transplant recipients significantly exceeded QOL scores for diabetic KTA recipients (42). Pancreas transplantation, however, consistently improved patient perceptions of health, health management, and diet flexibility (42,43).

Matas *et al.* (43) examined whether the QOL among SPK transplant recipients changed with time. The average scores on SF-36 questionnaires for diabetic transplant recipients (SPK transplantation and KTA) were higher than the reported normal values for patients with congestive heart failure, chronic obstructive pulmonary disease, or depression and were similar to those for patients with hypertension. The timing of QOL assessments may be exceedingly important in determination of the effects of SPK transplantation. In one study, SPK transplant recipients rescored their pretransplantation QOL significantly lower after transplantation, compared with scores before the procedure (44). In general, there is a QOL benefit from the transplant procedure and the additional QOL improvements attributable to the pancreas transplant itself focus on the obvious transition from the diabetic state to a nondiabetic state.

Nephropathy

Obviously, a successful dual transplant with a pancreas and a kidney is one means of treating nephropathy in type 1 DM. However, most studies comparing renal function among SPK transplant recipients *versus* diabetic KTA recipients did not demonstrate significant differences during the early posttransplantation time period (45,46), although diabetic KTA recipients may readily redevelop microalbuminuria after transplantation (47). The lack of long-term renal graft data has led to a greater reliance on histologic studies comparing SPK transplant and diabetic KTA recipients.

Mesangial expansion is the hallmark of clinical diabetic nephropathy. Therefore, its presence heralds recurrent diabetic nephropathy in allografts. SPK transplant recipients are less likely to display the pathologic changes of diabetic nephropa-

thy early after transplantation, compared with diabetic KTA recipients (48). Moreover, PAK transplantation seemed to prevent the development of diabetic nephropathy in biopsy samples from individuals who underwent PAK transplantation 1 to 7 yr after successful KTA (49,50). This suggests that even late restoration of normoglycemia may have significant beneficial effects on intrarenal architecture.

Ophthalmologic Manifestations of DM

The Diabetes Control and Complications Trial (4) suggested that restoration of tight glycemic control led to biphasic effects on retinopathy. There was an exacerbation of retinopathy early after the restitution of glycemic control. This was followed by a late phase of retinopathy stabilization and even mild improvement. It could be anticipated that SPK transplantation would have the same effect. In fact, 20 to 35% of PTA and SPK transplant recipients demonstrate early deterioration of retinopathy after the transplant event. Severe proliferative diabetic retinopathy, treated with pan-retinal laser therapy, was a common peritransplantation finding in most studies (51). The severity of these ophthalmologic changes may obviate a clear salutary effect of PTA or SPK transplantation on retinopathy. Alternatively, the correction of uremia alone with SPK transplantation or KTA among diabetic individuals may improve retinopathy, thus complicating analyses comparing the two. Nevertheless, a number of controlled studies described stabilization or clear improvement of retinopathy after successful SPK transplantation, especially when retinopathy was in its early stages, without exposure to laser treatment (52,53). The studies also described a corollary finding; SPK and pancreas transplant recipients experienced less deterioration of their retinopathy than did diabetic KTA recipients (52,53).

Visual acuity is variable after PTA and SPK transplantation, however. It remains stable in the majority of patients but can deteriorate or fluctuate in up to 30% of PTA and SPK transplant recipients (54). Preretinal macular fibrosis, vitreous hemorrhage, diabetic retinopathy severity, and grade and type of cataract all affect visual acuity after transplantation. Notably, all forms of cataracts increased after transplantation in almost every study that examined this parameter among PTA and SPK transplant recipients with time (55). Therefore, in the absence of severe retinopathy, PTA or SPK transplantation can stabilize or improve DM-related ophthalmologic findings. However, visual acuity may vary as a result of other associated ophthalmologic disorders (notably cataract formation) after pancreas transplantation.

Peripheral Vascular Disease

Two major factors likely influence peripheral vascular disease after PTA and SPK transplantation. The duration of DM before transplantation certainly increases the risk for posttransplantation macrovascular disease. In addition, hyperinsulinemia, with its theoretical atherogenic risks, could exacerbate macrovascular disease. Unfortunately, there have been no controlled trials evaluating the effects of PTA and SPK transplantation on type 1 DM macrovascular complications after transplantation. In general, lower-extremity peripheral vascular occlusive disease remains stable after kidney transplantation (56). Not surprisingly, Monaco and colleagues (15) suggested that euglycemia after SPK transplantation did not improve peripheral vascular disease. A surrogate measure for significant lower-extremity vascular disease is the amputation rate among at-risk individuals. Pancreas transplantation did not significantly affect lower-extremity amputation rates in the largest retrospective study examining this subject to date (57). These findings suggest that, despite the improvements in lipid profiles among pancreas transplant recipients (6), other risk factors may inhibit improvements in macrovascular disease and that macrovascular complications may be differentially affected by pancreas transplantation, in contrast to many of the microvascular complications of DM.

Hypertension

Hypertension is a major risk factor for coronary artery disease and commonly affects individuals with DM. Several small studies have examined whether SPK transplantation alters the prevalence of posttransplantation hypertension, with mixed results. Data from the early 1990s suggested that 60% of SPK transplant recipients exhibited posttransplantation hypertension, with 15 to 30% rates of BP improvement after SPK transplantation (58,59). Improvement was defined as a reduction in the number of BP medications or improvement in measured BP. Unfortunately, nocturnal BP remained significantly elevated, suggesting that 24-h BP control merited greater attention among hypertensive SPK transplant recipients (60). Recent data suggested that the prevalence of post-SPK transplantation hypertension may be decreasing (only 40%) with the increasing use of TAC and MMF after SPK transplantation (61).

Some authors have suggested that the type of pancreatic exocrine drainage could affect the prevalence of post-pancreas transplantation hypertension. BD leads to urinary losses of sodium and bicarbonate, with a constant state of mild volume depletion and metabolic acidosis. Indeed, hypertension seems to be more common with primary ED, compared with BD (62). However, conversion from BD to ED is not associated with an increase in BP (62). This suggests that factors other than those noted above have greater effects on post-PTA or SPK transplantation BP than previously suspected.

Cardiovascular Disease

Early reports suggested that there was no improvement in cardiac risk among SPK transplant recipients (63). Indeed, a history of preexisting myocardial dysfunction or congestive heart failure significantly increased the mortality risk after pancreas transplantation (63). With greater experience, patients with lower cardiac risks were selected for PTA and SPK transplantation. It is not surprising, therefore, that cardiac death rates for SPK transplant recipients are now equivalent to or better than cardiac death rates for other transplant recipients with type 1 DM (27). Certainly, individuals with histories of coronary artery disease and revascularization procedures are potential candidates for pancreas transplantation. However, their cardiac death rates remain significantly greater than those

for individuals without pretransplantation coronary artery disease (relative risk, 4.3; $P < 0.001$) (14). Such information is important for patient counseling as well as the establishment of optimal post-PTA or SPK transplantation cardiac follow-up monitoring.

The transplant itself may affect cardiac function. Data from several small studies suggested that pancreas transplantation improved echocardiographically measured left ventricular systolic and diastolic function, as well as left ventricular geometry (64,65). These physical changes seem to occur in concert with improvements in cardiac autonomic function (66). Overall, among individuals at low risk, PTA or SPK transplantation seems to provide some demonstrable benefits with respect to cardiac function. Long-term, prospectively collected data will be necessary to definitively establish whether pancreas transplantation has beneficial effects on coronary artery disease after transplantation.

Neuropathy

The effects of PTA and SPK transplantation may be most evident in evaluations of the improvement of diabetic neuropathy after transplantation. SPK transplantation leads to rapid initial improvement and at least stabilization of peripheral diabetic neuropathy (42,67). Serial action potential amplitude studies of the median, ulnar, peroneal, and tibial nerves, as well as orthodromic sensory conduction velocity studies, demonstrated improvement by 6 mo after transplantation (68). Interestingly, action potential amplitudes (a measure of nerve fibers capable of conducting impulses) demonstrated prolongation of recovery after SPK transplantation, with improvements extending for at least 5 yr and potentially continuing for as long as 8 yr after transplantation (69). Autonomic function also demonstrated long-term improvement, with the greatest recovery being evident 8 yr after transplantation (42,69). These findings demonstrate significantly greater improvements than those observed for diabetic KTA recipients, and they mimic the improvements in neuropathy observed in the Diabetes Control and Complications Trial (4).

Sexual Dysfunction and Reproduction

Sexual dysfunction is a common complication that affects approximately 50 to 75% of all individuals with DM and renal failure. Erectile dysfunction is a primary complaint among diabetic male patients, affecting 75 to 90% of all such men, especially those with renal disease. Female sexual dysfunction is just as common in DM and is manifested in a similar way, with decreased vaginal lubrication in response to stimulation, failure of normal genital engorgement, and loss of orgasmic potential (70). There are minimal data examining whether PTA or SPK transplantation improves sexual dysfunction after transplantation. Among men, there is actually a risk that the surgical dissection for the procedure could precipitate erectile dysfunction. However, at least in one study, SPK transplantation was associated with modest improvements in erectile function, although a large percentage of male SPK transplant recipients still required at least one additional therapy to improve sexual function (71).

Unfortunately, there are no data available to indicate whether pancreas transplantation restores female sexuality. However, there are data demonstrating that pancreas transplantation is associated with fertility in women. The National Transplantation Pregnancy Registry recently reported on a group of 18 SPK transplant recipients whose 23 pregnancies resulted in 20 live births (72). Prematurity and low birth weight occurred in 70% of the pregnancies. The children, however, were developing well at the time of the last follow-up examinations. Hypertension complicated the pregnancies (91% frequency), as did urinary tract infections (70% frequency). Notably, 25% of the mothers also were preeclamptic and two recipients lost three grafts (one kidney transplant and one SPK transplant) within 2 yr after the pregnancy.

One additional risk complicating pregnancy after SPK transplantation involves the potential teratogenic effects of certain immunosuppressive agents. TAC, CsA, and azathioprine are all safe for use during pregnancy. Unfortunately, despite its profound effect in transplantation, there is limited information regarding the use of MMF during pregnancy. It was associated with adverse developmental effects in preclinical studies. Therefore, although case reports of successful pregnancies during MMF therapy have been documented (73), at this time it is not recommended that women continue MMF treatment during pregnancy or during periods when they anticipate becoming pregnant. Clinical practice dictates the substitution of azathioprine for MMF in these instances. Finally, 17 male SPK transplant recipients have fathered 20 pregnancies to date, without major complications (72). Therefore, it is possible for SPK transplant and PTA recipients to safely bear children after the transplant event, although these are definitely high-risk pregnancies. Whether transplantation has direct effects on fertility requires further analysis.

Summary

The advantages of PTA and SPK transplantation are now more obvious as improvements in surgical techniques and new immunosuppressive agents have made an increasing number of PTA and SPK transplants viable and functional in the long term. The obvious benefits of normoglycemia would theoretically be even more profound if it becomes possible to perform PTA for patients without significant renal dysfunction or for patients early in the progression of DM-related renal disease. Nevertheless, SPK transplantation can be touted as a therapeutic advance for type 1 DM. It can improve survival rates and limit many DM-related complications, while improving QOL. The effects of SPK transplantation and PTA on other aspects of DM, *e.g.*, advanced glycosylation end products and lipid profiles, are also intriguing (6,61,74,75). More studies must be performed to determine whether early changes in these metabolic and biochemical parameters predict good outcomes after SPK transplantation and PTA. Finally, the recent study by Shapiro *et al.* (76) again raises the question of why the whole pancreas should be transplanted. Their provocative article suggested that islet cell transplantation may be a feasible form of transplantation in the near future. It is hoped that islet cell transplantation will convey the same benefits, with respect to

survival rates and diabetic complications, as do PTA and SPK transplantation today. This transplantation approach to the treatment of type 1 DM is the first real alternative to insulin therapy. It does carry the risks of immunosuppression, and it is unable to eradicate the consequences of preexisting disease. However, PTA and SPK transplantation, and perhaps islet cell transplantation in the future, bring with them the possibility for normoglycemia and restoration of a sense of normalcy to life for individuals with type 1 DM.

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