

## PANCREAS TRANSPLANTATION: INDICATIONS, CLINICAL MANAGEMENT, AND OUTCOMES

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### 1. ABSTRACT

Although many advances have been made, pancreas transplantation still poses several challenges to the surgeon, internist and patient. With success rates now above 80% and improving yearly, diabetic patients must make a major life-style decision when considering a pancreas transplant. The main concerns are will the benefits of insulin-independence off-set the risks of surgery and immunosuppression. For diabetics near dialysis and considering a kidney transplant, the decision may not be as difficult. However, for those patients who are failing insulin therapy (brittle control) and remain with good renal function, the options are limited. As the success of pancreas transplantation improves, the procedure may become routine at more centers and become accepted by more third-party carriers. However, as with other solid organs, the availability of pancreases is limited and the supply soon to be exhausted. Thus, further advances are required for the prevention and treatment of Type 1 diabetes. Hopefully, the new frontiers of the next century will allow physicians to identify and preventively treat those at risk for the development of diabetes. Thus, the population of patients suffering from the consequences of this dreadful disease will be greatly reduced. With new developments in immunosuppression and islet transplantation, diabetic patients of the future may be offered the option of a procedure with reduced risks, less morbidity, and improved long-term cure rates.

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### 2. INTRODUCTION

Until the late 1960's, various methods of exogenous insulin therapy were the sole means of treating Type 1 (insulin-dependent) diabetes mellitus. However, during the past three decades, many advances have been made in the surgical approach to the treatment of this disease entity. The first pancreas transplant was performed by Kelly and Lillihei in 1966 and during the ensuing 7 years, 14 additional transplants were performed by this team (1). While the initial results were quite dismal, the efforts of these surgeons demonstrated that successful pancreas transplantation could achieve insulin-independence and that long-term function (up to 1 year) was possible. Since then, new immunosuppressive agents and advances in surgical technique have improved outcomes. By 1996, a total of over 8,800 pancreas transplants have been performed world-wide with insulin independence rates at 1 year surpassing 80% in some recipient categories (2,3). The following review discusses the evolution of pancreas transplantation and demonstrates how improved surgical technique combined with the development of newer immunosuppressive agents have contributed to the efficacy of this procedure as a cure for Type 1 diabetes.

### 3. INDICATIONS

Although debatable, pancreas transplantation has not been advocated by most physicians as a preventative measure for the complications of diabetes. Thus, pancreas transplantation is mostly reserved for those Type 1 diabetic patients who suffer from the secondary complication of end-stage nephropathy and need a kidney transplant (4). The quality of life associated with insulin therapy must be worse than that which can be achieved by being free of diabetes and on immunosuppression in order

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for a non-uremic diabetic to be considered for a pancreas transplant (5). Thus, pancreas alone transplantation is limited to those patients who have difficult control of blood sugars and experience frequent episodes of hypoglycemic unawareness (2). Nearly all diabetic patients with end-stage renal disease or advanced nephropathy (creatinine clearance  $\leq 50$  ml/min) are candidates for a pancreas transplant, unless the risks for surgical complications are too great (6). In diabetic recipients of kidney transplants, patients already assume the risks of immunosuppression. Therefore, only the morbidity of a surgical complication is added by a pancreas transplant. Options which uremic diabetics can consider include a cadaveric or living-donor kidney transplant followed later by a cadaveric or living-related (hemi-) pancreas, simultaneous cadaveric kidney/whole pancreas transplant, or living-related donor simultaneous kidney/segmental (tail) pancreas transplant (7).

While almost all diabetics with end-stage renal disease are candidates for transplantation, a few exclusion criteria do exist. Malignancy, active infection, ongoing substance abuse, major psychiatric illness, and the inability to understand the nature of the transplant or to comply with follow-up are considered absolute contraindications (8). However, relative contraindications vary among institutions. Most centers consider non-revascularizable cardiovascular disease, blindness, severe peripheral vascular disease, hypertension, age greater than 45 years, excess weight, and history of medical non-compliance as relative contraindications. In a study performed at our institution, uremic diabetic patients who are eligible for transplantation demonstrated lower perioperative risks when obtaining a preoperative cardiac evaluation. Furthermore, the study showed that the group most likely to benefit from this approach were those patients who had diabetes for greater than 20 years and had absent symptoms (i.e. angina, shortness of breath, etc.) of coronary artery occlusive disease. However, controversy remains among cardiologists in their approach to this sub-group of patients. Some cardiologists believe that stress thallium scans in this patient population are at risk for many false-negative results. Thus, the gold-standard of coronary angiography is recommended for evaluation of cardiac perfusion. Based on the same analysis, exclusion of patients with histories of peripheral vascular disease was not justified. Benefits of pancreas transplantation were still apparent in patients with cerebral vascular accidents or transient ischemic attacks and those who underwent peripheral vascular procedures (either by-pass, angioplasty and/or major amputation). Blind diabetic patients seem to especially benefit from successful pancreas transplant at our institution. However, many centers will exclude such patients. The quality of life in blind diabetics improves dramatically by eliminating the risks of

incorrect insulin dosing or blood sugar monitoring and by reducing their dependency on others regarding basic activities of daily living. In this same analysis, hypertension did not affect graft outcome. However, patient age greater than 45 years and/or excess weight did increase the risk of technical failure in some subgroups of patients.

## **4. ORGAN AVAILABILITY & CONTRAINDICATIONS TO DONATION**

Pancreata can be procured from virtually every available cadaver from which other organs are retrieved. Presently, the standard of practice is to obtain the kidneys, liver, and pancreas from a single donor. However, the pancreas can be technically difficult to procure due to its anatomical location and vascular anatomy. Rarely, the pancreas may not be recovered if the liver is at risk during organ procurement. Similarly, if small bowel transplantation continues to progress at its present pace, modifications in procurement technique will have to accommodate the shared blood supply of the small intestine and pancreas.

Contraindications to the use of a donor pancreas include history of diabetes mellitus (Types 1 or 2), malignancy, acute pancreatitis, injury to the pancreas occurring during procurement, and advanced donor age (9).

## **5. SURGICAL ADVANCES**

Pancreas transplantation became more successful as the technical approaches to the recipient procedure evolved. Many surgical considerations have been controversial and scrutinized over the past several years due to the complexity of the procedure. Technical decisions are made regarding: 1) whole vs. segmental graft transplantation, 2) pancreatic ductal obliteration vs. drainage of exocrine function (i.e. digestive secretions), 3) bladder vs. enteric drainage, 4) use of a duodenal segment vs. a duodenal patch, 5) intra-peritoneal vs. retro-peritoneal placement of the graft. The drainage of exocrine secretions evolved from ureteral drainage to its present and most common form -- bladder drainage (10-12). In 1984, Ngheim and Corry introduced the duodenal-bladder drainage technique (12). This technique relies on the use of a segment of graft duodenum which is anastomosed to the bladder in a side-side fashion. The proximal and distal ends of the duodenal segment are then sutured and/or stapled closed. Arterial blood supply to the pancreas is obtained from the recipient iliac artery either by direct anastomosis to the donor splenic and superior mesenteric arterial segments or via a Y-graft consisting of a short segment of donor artery which is interposed between the pancreas graft and recipient artery. Venous return is obtained from a segment of graft portal vein which drains into the recipient iliac

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**Table 1. Categories used for the international transplant registry analysis**

DONOR	
<b>LRD</b>	<i>Living related donor</i>
<b>CAD</b>	<i>Cadaveric donor</i>
RECIPIENT	
<b>PTA</b>	<i>Pancreas transplant alone</i>
<b>PAK</b>	<i>Pancreas after kidney</i>
<b>SPK</b>	<i>Simultaneous pancreas/kidney</i>
DRAINAGE	
<b>BD</b>	<i>Bladder drainage</i>
<b>UD</b>	<i>Ureteral drainage</i>
<b>ED</b>	<i>Enteric drainage</i>
<b>DI</b>	<i>Ductal injection</i>

vein. Excellent illustrations of the operative procedures for a simultaneous cadaveric kidney/pancreas transplant appear in reference 13.

### 6. IMMUNOSUPPRESSION & MONITORING

The introduction of bladder drainage into the recipient procedure has a two-fold advantage. First, the technique allows for safe, effective drainage of exocrine secretions. Second, it also allows for monitoring of graft function, and therefore, rejection (14). Urinary amylase can be monitored and a rejection episode suspected when amylase levels fall by at least 50% (15,16). Additionally, a rise in serum pancreatic enzymes often precedes or occurs concordantly with falling urinary amylase levels (17,18). However, elevated serum enzymes can be a reflection of graft pancreatitis, possibly due to urinary reflux, and thus, a biopsy diagnosis may be required (see below). Rising serum enzymes should first be managed by relieving intra-bladder, urinary pressures; accomplished by placement of a urethral catheter.

For recipients of simultaneous pancreas/kidney transplants, serum creatinine levels remain the most sensitive marker for rejection. Rarely, a discrepancy in rejection of either the kidney or pancreas graft occurs. This situation requires close monitoring of serum creatinine and urinary amylase levels. Both markers are followed until function of the grafts stabilize. In cases of pancreas alone recipients, declining urinary amylase levels and/or rising serum amylase levels are the only indicators of graft rejection and a biopsy is usually required to confirm the diagnosis. To obtain a biopsy specimen, cystoscopic transduodenal or CT guided approaches are

available (19-22). These procedures have been found to be both safe and reliable.

During the early years of transplantation, immunosuppression consisted of a steroid combined with azathioprine. However, a new era began with the introduction and wide-spread use of cyclosporin during the 1980's. Since that time a few additional agents have become part of the armamentarium in the fight against rejection. Most centers now use quadruple therapy consisting of an inducing agent given at the time of transplantation (usually an anti-lymphocyte gammaglobulin) followed by maintenance immunosuppression of azathioprine or mycophenolate mofetile, cyclosporin or tacrolimus, and a tapering dose of steroids (23,24). The development of new immunosuppressive agents is a field filled with exciting potential and may soon bring forth compounds which will eliminate the need for some of the existing drugs and thus eliminate many of their hazardous side-effects.

### 7. PATIENT AND GRAFT SURVIVAL

The International Pancreas Transplant Registry, housed at the University of Minnesota, collects and evaluates patient information submitted from around the world (2,3). In 1995, 1156 pancreas transplants were reported to the registry with over 1000 performed in the United States. Since 1966, the total number of cases reported are 6429 for North America, 2102 for Europe, 74 in Australia, 53 in Asia, 21 in South America, and 2 in Africa. For purposes of analysis, patients are categorized according to recipient-status, donor-status, and type of drainage procedure (Table 1). Overall, bladder drainage has the lowest technical failure rate (8%) compared to enteric (11%) and duct occlusion (23%) techniques (2,3). Furthermore, bladder drainage has improved graft survival in both the United States and Europe. In the most recent analysis, graft loss from rejection at one year for PTA and PAK patients was 6 and 9%, respectively, compared to 3% for SPK recipients. Comparable kidney allograft survival for SPK patients and matched diabetics who received kidney allografts only (80% vs. 86%) are also seen. When data is not censored for graft loss due to technical failure or patient death with a functioning graft, over-all graft survival at 1 year now approaches 81% for PTA recipients, 71% for PAK recipients, and 64% for SPK recipients. HLA matching has no apparent impact on graft loss in SPK recipients. However, an increasing number of haplotype mismatches in PTA and PAK recipients is associated with a higher rate of graft loss in technically successful cases. Preservation data demonstrates that cold storage has minimal influence. Thus, pancreases can be safely stored at 4°C for 24-30 hours.

At our institution, we recommend that uremic Type 1 diabetics consider a living related kidney first, followed by a cadaveric pancreas (25,26). This approach

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eliminates the stress of dialysis at the time of pancreas transplantation. For this sub-group of patients, insulin-independence at one year as reported to the registry for 1994-1995 was 79% and similar to SPK recipients (2). Overall patient survival at one year is just over 90% in all recipient categories.

### **8. QUALITY OF LIFE**

Successful pancreas transplantation has been shown in many studies to improve patient quality of life, especially those with brittle control of their diabetes (27,28). For patients with functioning PTA grafts, approximately 90% stated that they were healthier after their pancreas transplant. Furthermore, 92% stated that managing immunosuppression was much easier than controlling their diabetes with insulin and glucose monitoring. With respect to demands on other family members, 63% of patients stated that diabetes was more time consuming than the transplant, 29% about equal, and 9% stated that managing immunosuppression required more involvement of others. For SPK recipients with functioning grafts, dramatic changes in life-style occur due to the elimination of the need for dialysis and insulin-injections.

### **9. EFFECTS ON COMPLICATIONS OF DIABETES**

Studies evaluating the effects of pancreas transplantation on the secondary complications of diabetes have demonstrated variable results. With respect to retinopathy, data from our center determined that retinopathy was advanced in most recipients and that visual defects progressed within the first three years after transplant in about 30% of patients whether or not the pancreas graft continued to function (29). However, after three years, retinopathy stabilized as long as the graft continued to function. As expected, if the graft failed, retinopathy was likely to progress. A later study from the University of Wisconsin compared several parameters of diabetic retinopathy in SPK recipients and recipients of isolated kidney allografts (30). Their results showed significant improvement of retinopathy in SPK patients. However, those recipients with advanced retinopathy at the time of transplantation did not show improvement or early stabilization. Other studies show subjective improvement of neurological deficits, however, these findings do not correlate with quantitative measurements of nerve conduction (31-33). Difficulty arises when attempting to distinguish the effects on nerve conduction of improved glucose control versus improved creatinine clearance in SPK recipients. Additional reports on SPK patients show dramatic subjective but not quantitative improvement in autonomic neuropathy and gastroparesis (33,34). Functioning pancreas transplants stabilize diabetic glomerular nephropathy in native kidneys and prevent the recurrence of renal microvascular changes in renal allografts (35). However, cyclosporin and tacrolimus have nephrotoxic side-effects and thus, chronic glomerular

damage can still occur. Improvements in the peripheral microvascular disease of pancreas allograft recipients are also difficult to evaluate (36). Enhanced skin perfusion has been demonstrated by laser studies, however, a decrease in skin ulceration or the need for amputation has yet to be shown.

### **10. COMPLICATIONS**

The decision to undergo a pancreas transplant requires a major commitment from both the surgeon and patient. The procedure is at risk for complications due to its technical difficulty combined with the inherent nature of the gland itself. Due to the conditions of the vascular anastomoses and the low-flow state of the pancreas, we recommend the use of low-dose anticoagulation (heparin or dextran) post-operatively (37). While the risk of post-operative bleeding is less than 5%, the risk for graft thrombosis is virtually eliminated. Post-operative hematuria is common but usually stops spontaneously. However, cystoscopic cauterization may be required for persistent bleeding. The most serious problems encountered post-operatively are leaks from the lateral duodenal suture (staple) lines or the duodenal/bladder anastomosis (38). Breakdowns at these sites occur secondary to technical problems (early) or chronic ulceration (late). Conservative management (urethral catheter drainage) usually controls small leaks and allows for spontaneous healing and closure. However, larger leaks usually require abdominal exploration and anastomotic repair. Dependent on the situation which is encountered surgically, some patients may require either conversion to enteric drainage or graft pancreatectomy (39). Small bowel obstruction, incisional hernia, lymphocele, enterocutaneous fistula, and graft thrombosis are other problems included in the list of complications which occur with far less frequency.

A high rate of early infection in pancreas transplant recipients has been reported by Sollinger, et. al. (40). Their study showed that approximately 82% of SPK patients have at least one episode of infection (91% immunological and 9% surgical) while on quadruple immunosuppression (ALG, AZA, CSA, and prednisone). These early infections are surgically related and can present as intra-abdominal abscesses, wound infections, anastomotic leaks, and urinary tract infections (most common). Most urinary tract infections will respond to prompt initiation of antibiotic therapy. However, cystoscopic evaluation is required for a persistent or recurrent urinary infection. In such cases, a nidus for infection is usually identified and removal of an anastomotic staple or suture eliminates the cause. Conversion to enteric drainage may be warranted for patients with persistent UTI and no identifiable source (39). Late infections by a variety of opportunistic microbes are usually related to immunosuppression. The most common organisms involved in superficial and deep wound infections are staphylococcus species (56%) and candida species (33%) (41). In a report from our center,

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intra-abdominal fungal infections were as high as 9% and associated with significant morbidity and mortality (42). Furthermore, patients on dialysis (either hemo- or peritoneal-) prior to transplant were at significantly higher risk for developing an intra-abdominal infection (43). Thus, the risk of a higher infection rate further emphasizes the need to transplant this patient population when they first demonstrate evidence of renal failure and to not wait until they are debilitated by uremia and dialysis dependent.

Male patients are prone to urethritis and urethral strictures when the pancreas is bladder drained (40). The cause being chronic urethral irritation by pancreatic secretions (enzyme related). Temporary placement of a urethral catheter usually relieves the pain and discomfort a patient experiences. However, enteric conversion may be required for severe cases (39). Acid/base disturbances are another problem associated with pancreatic secretions and bladder drainage. Urinary bicarbonate losses can be corrected by an oral sodium bicarbonate regimen in most cases. However, severe imbalances may need enteric conversion to stabilize the base deficit (39).

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