Original Science

# Evolving Trends in Pancreas Transplantation: The Wake Forest Experience

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## Abstract

A single center experience with pancreas transplantation (PTx) over an 11+ year period is reviewed.

**Methods:** We retrospectively studied outcomes in 202 consecutive PTxs in 192 patients at our center; 179 PTxs (89%) were performed with portal-enteric and 23 with systemic-enteric drainage.

**Results:** From 11/01 to 3/13, we performed 162 simultaneous kidney-PTxs (SKPT), 35 sequential PTxs after kidney (PAK), and 5 PTx alone (PTA; 40 solitary PTxs [SPT]). With a mean follow-up of 5.5 years, overall patient (87% SKPT versus 87.5% SPT), kidney (74% SKPT versus 82.5% SPT) and pancreas graft survival (both 65%) rates were comparable. Causes of PTx loss were also similar between SKPT and SPT; the rates of early thrombosis were 8.6% and 5%, respectively. Acute rejection rates were similar between groups (SKPT 29% versus SPT 26%, p=NS). Surveillance PTx biopsy-directed immunosuppression has contributed to equivalent long-term outcomes in SKPT and SPT. Good results have been achieved in African-American patients and in patients with a type 2 diabetes phenotype.

**Conclusions:** Excellent five-year outcomes following PTx can be achieved as >86% of patients are alive, >87% of surviving patients are dialysis-free, 80% of surviving patients remain insulin-free, and 88% of surviving patients have detectable C-peptide levels

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## Introduction

Vascularized pancreas transplantation (PTx) was developed as a means to re-establish endogenous insulin secretion (C-peptide production) responsive to normal feedback controls and has evolved over time to a form of auto-regulating total pancreatic endocrine replacement therapy that reliably achieves a euglycemic state without the need for either exogenous insulin therapy or close glucose monitoring. A successful PTx is currently the only definitive long-term treatment that restores normal glucose

homeostasis in patients with complicated diabetes without the risk of either severe hypo/hyperglycemia and may prevent, stabilize, or possibly reverse progressive diabetic complications. As of December 2014, more than 48,000 PTxs were reported to the International Pancreas Transplant Registry.[1] PTx in diabetic patients is divided into 3 major categories; those performed simultaneously with a kidney transplant (SKPT), usually from a deceased donor; those performed after a successful kidney (PAK) transplant in which the kidney came from either a living or deceased donor; and PTx alone (PTA) in the complete absence of a kidney transplant. The latter 2 (PAK and PTA) categories are usually combined together as solitary pancreas transplants (SPT) because of similar outcomes and the absence of uremia at the time of transplant. The total number of PTxs steadily increased in the United States until 2004 but has since declined, particularly in the PAK category.[1,2] In the last decade, era analyses of national data have demonstrated that deceased donor recovery rates and additions to the waiting list have decreased; donor organ discard rates and recipient waiting times have increased; and the proportion of recipients who are older, African-American (AA), have a higher body mass index (BMI), or are characterized as having type 2 diabetes have all increased.[1-4] The majority (74%) of PTxs are performed as SKPTs whereas approximately 17% are performed as PAK and 9% as PTA transplants.[1-4]

With improvements in organ retrieval and preservation technology, refinements in diagnostic and therapeutic technologies, advances in clinical immunosuppression and antimicrobial prophylaxis, and increased experience in donor and recipient selection, success rates for PTx have steadily improved.[1-5] Improvements in outcomes are primarily due to significant reductions in technical failures and immunologic graft losses over time. For recipients of primary deceased donor PTxs, one-year patient survival is more than 96% in all 3 categories; unadjusted five-year patient survival rates are 90% in SKPT, 89% in PAK, and 90% in PTA recipients; and more than 70% of patients are alive at ten years post-transplant.[1-4] One-year PTx survival (insulin-free) rates are 85.4% in SKPT (95.5% kidney graft survival), 84.4% in PAK, and 82.7% in PTA recipients, which translates to pancreas graft half-lives approaching 14 years in SKPT and 10 years in SPT recipients.[1-5] In contrast to other treatments for diabetes, PTx survival is largely defined as complete freedom from exogenous insulin therapy concomitant with the absence of abnormal glycemic excursions. The purpose of this study was to review our single-center outcomes and trends in 202 PTxs spanning an 11-year experience in the new millennium.

## Methods

### Recipient Selection

Indications for PTx were insulin-requiring diabetes with complications and the predicted ability to tolerate the operative procedure and manage the requisite immunosuppression and expected follow-up irrespective of detectable C-peptide levels. Selection criteria for SKPT in type 2 diabetes included patients <55 years of age with a BMI <30 kg/m2, insulin-requiring for a minimum of 3 years with a total daily insulin requirement <1 u/kg/day, a fasting C-peptide level <10 ng/ml, absence of severe vascular disease or tobacco abuse, adequate cardiac function, and presence of "complicated" or hyperlabile diabetes.[6-8] Selection criteria for SPT were similar to SKPT except for renal function, in which the calculated abbreviated Modification of Diet in Renal Diseases (aMDRD) glomerular filtration rate (GFR) was >70 ml/min in PTA (native renal function) and >40 ml/min in PAK (renal allograft function) recipients. Donor selection was more stringent for SPT, including younger donors and a minimum of a 2-3 human leukocyte antigen (HLA) match.[6,9]

### Technical Aspects

The history of PTx has been largely defined by the evolution in surgical techniques. The first SKPT was performed at Wake Forest Baptist Medical Center (WFBMC) on 6/3/92.[6] The exocrine secretions were managed with bladder drainage using a donor duodenal segment conduit. The patient did well with excellent dual allograft function for 15 years although she did undergo enteric conversion on 12/20/07. The patient's kidney failed in 2008 secondary to chronic allograft nephropathy and she received a second deceased donor kidney transplant on 1/6/10. However, her original pancreas allograft continues to function well with excellent glycemic control 23 years following transplantation. No

other PTxs were performed at our center until November, 2001, and the above pancreas transplant is not included in this analysis.

Since November, 2001, all PTxs were initially approached as an intent-to-treat with portal-enteric drainage using an anterior approach to the superior mesenteric vein (SMV) and enteric drainage to the proximal ileum in the recipient (side to side duodeno-enterostomy, usually without a diverting Roux limb).[6,10] Arterial inflow was usually based on the recipient's right common iliac artery after the pancreas dual artery blood supply was reconstructed with a donor common iliac bifurcation "Y" graft. Of the first 121 SKPTs, all but two were performed by transplanting the kidney to the left iliac vessels and the pancreas to the right common or external iliac artery through a midline intraperitoneal approach. However, since 7/30/10, nearly all SKPTs were performed with ipsilateral placement of the kidney and pancreas to the right iliac vessels in order to reduce operating time and to preserve the left iliac vessels for future transplantation. All but 5 PTxs were performed from brain-dead donors; 5 SKPTs were performed from donation after cardiac death donors at our hospital in which extracorporeal support was used to assist in management of the donor after declaration of death by cardio-circulatory arrest.[11]

**Immunosuppression**

The first 37 patients received alternate day rabbit anti-thymocyte globulin (rATG) induction (1.5 mg/kg/dose, total 3-5 doses) in combination with tacrolimus (TAC), mycophenolate mofetil (MMF), and tapered corticosteroids.[12,13] Subsequently, 5 patients received a single dose (30 mg) of alemtuzumab (Alem) induction intra-operatively, 4 received both single dose Alem and rATG induction, and 16 received rATG induction. During this transitional period, 6 of these patients underwent early steroid elimination. From 2/05 through 10/08, 46 SKPT recipients (45 with portal-enteric drainage) were enrolled in a single center randomized trial comparing single dose Alem (30 mg intra-operatively over 2 hours) and multiple dose rATG (1.5 mg/kg/dose starting intra-operatively) induction in combination with TAC, MMF, and early steroid elimination.[14] rATG induction was administered on an alternate day basis (minimum of 3 doses administered, total cumulative dose 5-6 mg/kg). TAC was started immediately post-transplant at an oral dose of 1-2 mg twice daily every 12 hours. TAC dosing was titrated to achieve a 12 hour trough level of 10-12 ng/ml for the first 3 months post-transplant, then 8-10 ng/ml thereafter in the absence of rejection or toxicity. Oral MMF was begun immediately after transplant at 500 mg twice daily.

After rATG induction was completed, the MMF dose was increased to 2 gm/day in 2-4 divided doses. The MMF dose was reduced in patients with gastrointestinal intolerance or myelosuppression. After the first 3 months, the usual MMF dose was 1.5 gm/day in the absence of rejection. Corticosteroids were administered either as intravenous methylprednisolone 500 mg or intravenous dexamethasone 100 mg during surgery with subsequent doses given as premedication for rATG. Steroids were completely stopped on post-operative day #5 unless the patient was identified as “high immunological risk” defined by the presence of delayed (kidney) graft function, retransplantation, AA patient <40 years of age, allosensitization (pre-transplant panel reactive antibody [PRA] level >20%), or PTA. Since 2009, all PTx recipients at our center (n=74) have received Alem induction with TAC, MMF, and either early steroid elimination or rapid prednisone taper (dose reduction to 5 mg/day by 2 months following PTx if determined to be high immunological risk).[6, 14]

**Infection Prophylaxis**

All patients received anti-infective prophylaxis with fluconazole, valganciclovir, and trimethoprim-sulfamethoxazole.[6,12,14] Perioperative antibiotic prophylaxis consisted of a single pre-operative dose, an intra-operative dose, and 2-3 postoperative doses of cefazolin (1 gram intravenous). Patients received single-strength trimethoprim-sulfamethoxazole 1 tablet every Monday-Wednesday-Friday for at least 12 months as prophylaxis for Pneumocystis jiroveci. Anti-fungal prophylaxis consisted of oral fluconazole (50-100 mg/day) for 1-2 months. Anti-viral prophylaxis included oral valganciclovir 450 mg/day for 3 months (with dosage adjustments for renal dysfunction and leukopenia) when either the donor or recipient was cytomegalovirus (CMV) seropositive or both were CMV

seronegative. If the donor was CMV seropositive and the recipient seronegative (primary CMV exposure), then oral valganciclovir 900 mg/day (with dosage adjustments as above) was given for 6 months.[6,12,14]

**Diagnosis and Treatment of Rejection**

The diagnosis of renal allograft rejection was suggested by an unexplained rise in serum creatinine level of >0.3 mg/dl or a 25% increase from baseline level and confirmed by ultrasound-guided percutaneous biopsy. Banff criteria were used to determine the grade of rejection.[15] Since March, 2008, all SKPT patients underwent both reperfusion and 1 month surveillance kidney biopsies unless there was a specific contraindication. The diagnosis of pancreas allograft rejection was suggested by an unexplained rise in serum amylase, lipase, or glucose levels and confirmed by ultrasound-guided percutaneous biopsy. Treatment of rejection was based upon the Maryland Classification System,[16] and more recently the Banff 2007 Schema.[17] Borderline and mild pancreas allograft rejection episodes were treated with steroids whereas all other grades of pancreas rejection were treated with rATG. Follow-up pancreas allograft biopsies were performed to document histological improvement and response to therapy. Biopsies graded as "Indeterminate" were managed by optimizing maintenance immuno-suppression with follow-up biopsies as above. Following SPT, surveillance pancreas biopsies were performed at 3 week intervals until there were 2 consecutive normal biopsies.[18] Clinical biopsies were prompted by biochemical parameters.

**Statistical Analysis**

Data were compiled from both prospective and retrospective databases, with confirmation by medical record review in accordance with local Institutional Review Board guidelines and approval. Categorical data were summarized as proportions and percentages and continuous data were summarized as means and standard deviations. Univariate analysis was performed by the unpaired t test for continuous variables, the chi-square test for categorical variables, and Fisher's exact test when data were sparse. Unadjusted actual patient and graft survival rates were reported, and actuarial and death-censored graft survival rates were also determined. Pancreas graft survival was defined as complete insulin independence with normalization of hemoglobin A1c (HbA1c) levels. Survival curves were computed using the Kaplan-Meier method and compared using the log-rank test. A two-tailed p-value of $<0.05$ was considered to be significant.

## Results

From 11/1/01 through 3/1/13, a total of 202 PTxs were performed in 192 patients, including 162 SKPT, 35 sequential PAK, and 5 PTA (40 SPTs). 186 PTxs (92%) were primary and 16 pancreas retransplants (10 of which had their primary PTx performed at our center). All but 4 patients received kidney and PTxs either simultaneously or sequentially (one patient received a kidney following a PTA). In addition, 6 patients (3%) underwent subsequent kidney retransplantation. PTx with portal-enteric drainage was performed preferentially; however, systemic-enteric drainage was performed in 23 cases (11%) in which portal-enteric drainage was not deemed possible or safe. Indications for systemic-enteric drainage were pancreas retransplantation (n=9, in which the primary PTx was performed with portal-enteric drainage), central obesity (n=7), and difficult vascular anatomy (n=7).

**SKPT versus SPT**

We compared outcomes in 162 SKPT and 40 SPT recipients. Demographic characteristics for SKPT versus SPT were mostly comparable (Table 1); however, the SPT group had fewer HLA mismatches (SKPT mean 4.5 ± 1.2 versus SPT 2.7 ± 1.5, $p<0.001$), younger donors (SKPT mean 27 ± 11 versus SPT 22 ± 7.6 years, $p=0.004$), fewer AA recipients (SKPT 22% versus SPT 8%, $p=0.03$), shorter waiting time (SKPT mean 10 months versus SPT 6 months, $p=0.002$) but more retransplants (SKPT 1.2% versus SPT 35%, $p<0.001$). With a mean follow-up of 5.7 versus 7.7 years (p=NS), overall patient (86% SKPT versus 87% SPT), kidney (74% SKPT versus 80% SPT) and pancreas graft survival (both 65%) rates were comparable (Table 1 and Figures 1-2). The most common causes of pancreas graft loss were death with a functioning graft (DWFG) in SKPT and acute/chronic rejection in SPT recipients. Rates of early thrombosis were 8.6% in SKPT and 5% in SPT patients. The cumulative incidence of clinically evident, biopsy proven kidney or pancreas acute rejection in SKPT was similar to the incidence of clinically evident, biopsy proven pancreas rejection in SPT (SKPT 29% versus

**Table 1:** Donor and Recipient Characteristics and Results According to PTx category

| Mean ± SD | SKPT N = 162 in 161 patients* | SPT N = 40 in 38 patients* | p-value |
|---|---|---|---|
| Donor age (years) | 27.3 ± 10.6 | 22 ± 7.6 | 0.004 |
| Donor BMI (kg/m$^2$) | 23.9 ± 1.4 | 23.5 ± 6.8 | NS |
| Donation after cardiac death donors | 5 (3.1%) | 0 | NS |
| Cold ischemia time (hours) | 16.2 ± 7.4 | 14.8 ± 3.8 | NS |
| HLA-mismatch | 4.5 ± 1.2 | 2.7 ± 1.5 | <0.001 |
| PRA >10% | 27 (16.7%) | 8 (20%) | NS |
| CMV Donor+/Recipient- | 45 (27.8%) | 11 (27.5%) | NS |
| Retransplant | 2 (1.2%) | 14 (35%) | <0.001 |
| Portal-enteric technique | 147 (90.7%) | 32 (80%) | 0.09 |
| | | | |
| Recipient age (years) | 42.7 ± 11.3 | 42.2 ± 8.7 | NS |
| Patients aged 50 or older | 42 (26.1%) | 8 (21.1%) | NS |
| Recipient gender: Male | 94 (58.0%) | 19 (50%) | NS |
| Recipient: African American | 36 (22.2%) | 3 (7.9%) | 0.03 |
| Recipient weight (kg) | 71.1 ± 13.5 | 70.7 ± 12.8 | NS |
| Dialysis history: Hemodialysis Peritoneal Dialysis None (preemptive) | 82 (50.9%) 42 (26.1%) 37 (23.0%) | NA | |
| Duration of pretransplant diabetes (years) | 25.3 ± 9.8 | 26.7 ± 7.7 | NS |
| Waiting Time (months) | 10.1 ± 6.3 | 5.8 ± 7.2 | 0.002 |
| | | | |
| Patient survival | 133/154 (86.4%) | 33/38 (86.8%) | NS |
| Kidney graft survival | 120 (74.1%) | 28/35 (80%) | NS |
| Pancreas graft survival | 106 (65.4%) | 26 (65%) | NS |
| Follow-up (months) | 68.7 ± 96 | 92.1 ± 37 | NS |
| Early thrombosis | 14 (8.6%) | 2 (5%) | NS |
| Acute rejection | 47 (29.0%) | 11 (27.5%) | NS |
| Death in first 4 years post-transplant | 10 (6.2%) | 0 | NS |
| Death with functioning grafts | 15 (9.3%) | 0 | 0.007 |

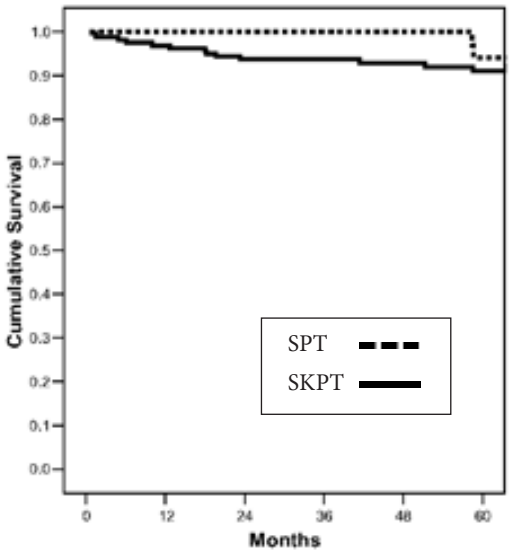
*One patients had 2 SKPTs, two had 2 SPTs, and seven had SKPT followed by SPTs at center.

SPT 27.5%, p=NS). With a mean follow-up of 72 months in 16 pancreas retransplants versus 65 months in primary PTx recipients, respective patient survival (95% versus 86%), kidney graft survival (82% versus 75%), and PTx graft survival (64% versus 65%) rates were comparable.

### SKPT in AA Recipients

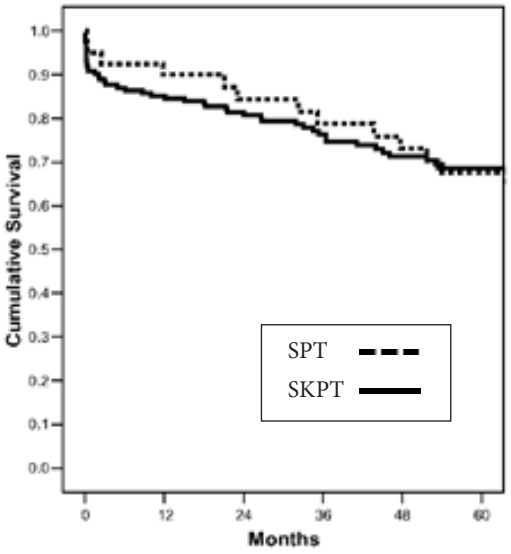
A total of 39 PTxs (36 SKPT, 2 PAK, and 1 PTA) were performed in AA recipients and the remaining 163 in non-AA recipients (161 Caucasian, 1 Asian, and 1 Hispanic). The AA group had a longer duration of pretransplant dialysis (mean AA 32 months versus 16 months non-AA, p=0.02),

**Figure 1:** Actuarial patient survival




Five-year actuarial patient survival according to type of pancreas transplant (N=162 SKPT versus 40 SPT, p=NS).

**Figure 2:** Actuarial pancreas graft survival




Five-year actuarial pancreas graft survival rates according to type of pancreas transplant (N= 162 SKPT versus 40 SPT, p=NS).

fewer preemptive transplants (5.5% AA versus 28% non-AA, p=0.004), fewer SPTs (8% AA versus 23% non-AA, p=0.04), more PTxs performed with systemic-enteric drainage (23% AA versus 9% non-AA, p=0.02), more patients with a current PRA ≥10% (28% AA versus 10% non-AA, p=0.008), more patients with 5-6 HLA mismatches (64% AA versus 42% non-AA, p=0.01), and fewer patients who were CMV seronegative at the time of PTx (28% AA versus 48% non-AA, p=0.03). In addition, the AA group had more patients with a body weight ≥80 kg (51% AA versus 24% non-AA, p=0.001), more patients with detectable pretransplant C-peptide levels (≥ 2.0 ng/ml) at the time of PTx (36% AA versus 14% non-AA, p=0.001), and more patients with a shorter duration (≤18years) of pretransplant diabetes (38% AA versus 17% non-AA, p=0.004). The latter 3 differences suggested that a type 2 diabetes phenotype was more prevalent in the AA group.

With a mean follow-up of 5.5 years, overall patient (90% AA versus 86.5% non-AA), kidney (67% AA versus 77% non-AA, p=0.21) and pancreas graft survival (59% AA versus 66% non-AA, p=0.35) rates were comparable. The rates of early PTx thrombosis (10% versus 7%) and early relaparotomy (46% versus 36%) were likewise comparable in the AA and non-AA groups, respectively. Cumulative clinical acute rejection rates were similar between groups (33% AA versus 27% non-AA). However, the incidence of death-censored dual graft loss was much higher in AA patients (22% AA versus 6% non-AA, p=0.01). In addition, the death-censored kidney graft survival rate (70% AA versus 87% non-AA, p=0.03) was lower in the AA group. In AA patients who were pretransplant C-peptide positive (n=14) versus C-peptide negative (n=25), there were no differences in mortality (7% versus 12%), kidney graft loss (21% versus 36%), or pancreas graft loss (36% versus 44%) rates, respectively.

**SKPT in "Type 2 Diabetes"**

We retrospectively analyzed outcomes in SKPT recipients who retained C-peptide production at the time of transplantation and had a type 2 diabetes phenotype. Over an 11+ year period, we performed 162 SKPTs including 132 in patients with absent or low C-peptide levels (<2.0 ng/ml, C-peptide "negative", including 21 with measurable C-peptide) and 30 in patients with C-peptide levels ≥2.0 ng/ml (C-peptide "positive", mean C-peptide level 5.7 ng/ml, range 2.1-12.4). At the time of SKPT, patients in the C-peptide positive group had a higher proportion that were age 50 years or older (40% versus 23%, p=0.06), had a later age of onset of diabetes mellitus (mean age 34 C-peptide positive versus 16 years C-peptide negative, p=0.0001), weighed more (mean 77 C-peptide positive versus 69 kg C-peptide negative, p=0.27), and had a greater proportion of AAs (47% C-peptide positive versus 17% C-peptide negative, p=0.001) compared to those in the group with no or low C-peptide levels (Table 2). Pre-transplant duration of diabetes was shorter in the C-peptide positive group (mean 17 years C-peptide positive versus 25 years C-peptide negative, p = 0.01) but duration of dialysis was longer (median 40 months C-peptide positive versus 14 months C-peptide negative, p=0.14). There were no significant differences between the two groups with regard to dialysis status, PRA, HLA-matching, and other pertinent characteristics.

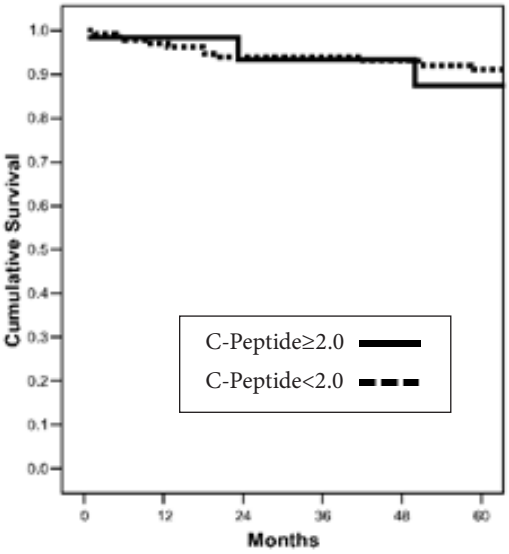
With a mean follow-up of 5.5 years, patient survival (87% C-peptide positive versus 85% C-peptide negative), kidney graft survival (77% C-peptide positive versus 72% C-peptide negative), and pancreas graft survival (57% C-peptide positive versus 66% C-peptide negative, all p=NS) rates were comparable between groups (Figures 3-5 and Table 2). Death-censored kidney (both 85%) and pancreas (61% C-peptide positive versus 77% C-peptide negative, both p=NS) graft survival rates were similar between groups. The incidence of death-censored dual graft loss was 11% in each group. The 4 deaths in C-peptide positive patients (1 early, 3 late) were due to an early surgical complication, hepatitis C virus infection with cirrhosis, and 2 malignancies, respectively. The incidences of early PTx thrombosis (3% versus 9.8%) and early relaparotomy (33% versus 36%) were no different in C-peptide positive and negative groups, respectively. At 5 years follow-up, there were no differences in acute rejection episodes (30% versus 29%), surgical complications, major infections, readmissions, HbA1c and C-peptide levels, or serum creatinine and calculated MDRD GFR levels between the 2 groups (Table 2).

**Table 2:** Donor and Recipient Characteristics and Results in C-peptide positive (≥2.0 ng/ml) versus C-peptide negative (<2.0 ng/ml) SKPT recipients

| Mean ± SD | C-peptide positive N=30 | C-peptide negative N=132 | p-value |
|---|---|---|---|
| Donor age (years) | 26.4 ± 11.3 | 27.5 ± 11.3 | NS |
| Donor BMI (kg/m$^2$) | 24.6 ± 4.1 | 23.7 ± 4.0 | NS |
| Cold ischemia (hrs): Kidney<br>Pancreas | 16.0 ± 4.4<br>15.6 ± 3.6 | 16.4 ± 4.8<br>16.4 ± 4.4 | NS<br>NS |
| HLA-mismatch | 4.7 ± 1.1 | 4.5 ± 1.1 | NS |
| PRA >10% | 8 (26.7%) | 19 (14.4%) | NS |
| CMV Donor+/Recipient- | 2 (6.7%) | 43 (32.6%) | 0.003 |
| Systemic-enteric technique | 7 (23.3%) | 8 (6.1%) | 0.008 |
| Recipient age (years) | 45.1 ± 10.2 | 42.4 ± 9.1 | NS |
| Patients aged 50 or older | 11 (36.7%) | 30 (22.7%) | 0.049 |
| Recipient gender: Male | 14 (46.7%) | 80 (60.6%) | NS |
| Recipient: African American | 13 (43.3%) | 23 (17.4%) | 0.006 |
| Recipient weight (kg) | 75.2 ± 13.2 | 70.2 ± 13.8 | NS |
| Recipient BMI ≥ 28 kg/m$^2$ | 12 (40%) | 18 (13.6%) | 0.003 |
| Dialysis type:<br>Hemodialysis<br>Peritoneal Dialysis<br>None (preemptive) | 22 (73.3%)<br>7 (23.3%)<br>1 (3.3%) | 61 (46.2%)<br>35 (26.5%)<br>36 (27.3%) | 0.0085<br>NS<br>0.0032 |
| Duration of dialysis (months) | 22.7 ± 14.5 | 26.1 ± 26.0 | NS |
| Years of insulin pre-SKPT | 14.9 ± 6.4 | 27.9 ± 8.6 | <0.01 |
| Daily insulin dose (units) | 45.4 ± 30 | 39.6 ± 18 | NS |
| Age of DM onset (years) | 30.4 ± 12.5 | 14.6 ± 8.9 | <0.01 |
| DM onset ≥ age 30 years | 15 (50%) | 7 (5.3%) | <0.001 |
| Diabetes duration ≤ 18 years | 18 (60%) | 13 (9.8%) | <0.001 |
| Waiting Time (months) | 10.1 ± 6.3 | 10.1 ± 6.4 | NS |
| Patient survival | 24 (80%) | 109/131* (83.2%) | NS |
| Death with functioning grafts | 2 (6.7%) | 14 (10.6%) | NS |
| Kidney graft survival | 19 (63.3%) | 91 (68.9%) | NS |
| Death-censored kidney graft survival | 19/27 (70.4%) | 91/111 (82.0%) | NS |
| Pancreas graft survival | 15 (50%) | 82 (62.1%) | NS |
| Death-censored pancreas graft survival | 16/27 (59.3%) | 82/117 (70.1%) | NS |
| Follow-up (months) | 56 ± 28 | 81.9 ± 41 | NS |
| Early thrombosis | 1 (3.3%) | 13 (9.8%) | NS |
| Initial length of stay (days) | 15.1 ± 12.0 | 12.3 ± 14.2 | NS |
| Acute rejection | 9 (30%) | 38 (28.8%) | NS |
| Death-censored dual graft loss | 6/27 (22.2%) | 14/110 (12.7%) | NS |
| Post-SKPT weight gain ≥5 kg | 17 (56.7%) | 36 (27.3%) | 0.004 |
| Latest C-peptide level (ng/ml)** | 5.0 ± 2.7 | 2.6 ± 1.7 | <0.05 |
| Latest HbA1c level (%)** | 5.6 ± 0.6 | 5.4 ± 0.8 | NS |

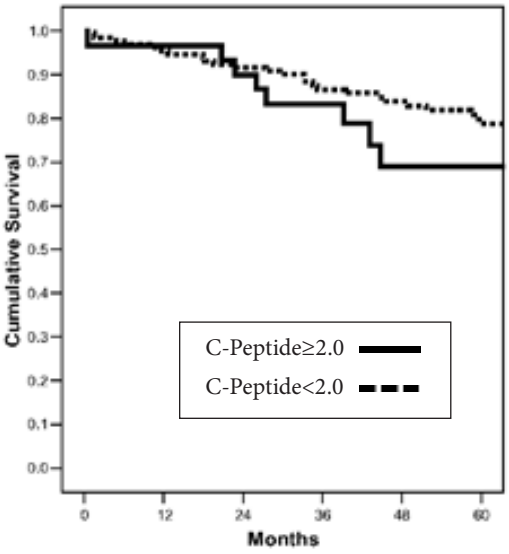
* One patient who eventually died underwent 2 SKPTs; ** In patients with functioning grafts

**Figure 3:** Actuarial patient survival



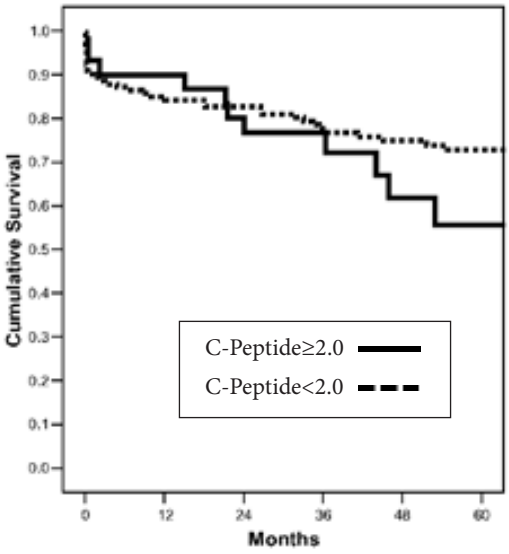

Actuarial patient survival in SKPT recipients stratified according to pretransplant C-peptide levels (N=132 C-peptide <2.0 versus 30 C-peptide ≥2.0 ng/ml, p=NS).

**Figure 4:** Actuarial kidney graft survival




Actuarial kidney graft survival in SKPT recipients stratified according to pretransplant C-peptide levels (N=132 C-peptide <2.0 versus 30 C-peptide ≥2.0 ng/ml, p=NS).

**Figure 5:** Actuarial pancreas graft survival




Actuarial pancreas graft survival in SKPT recipients stratified according to pretransplant C-peptide levels (N=132 C-peptide <2.0 versus 30 C-peptide ≥2.0 ng/ml, p=NS).

## Outcomes According to Different Measures of "Success"

The definition of PTx graft failure is not uniform, and "success" following PTx may be measured by a number of parameters, including freedom from exogenous insulin and dialysis, absence of hyper/hypoglycemia, enhanced well-being and quality of life, and improved life expectancy. With a mean follow-up of 5.5 years, overall patient survival for the entire series (n=192) was 86.5%. A total of 15 patients experienced DWFG whereas 3 patients died following kidney graft failure, 6 following PTx graft failure, and 2 following both kidney and PTx graft failure. Overall kidney graft survival was 75% and the death-censored kidney graft survival rate was 84%. Causes of kidney graft loss (n=49) included DWFG (n=21), chronic allograft nephropathy (n=12), acute/chronic rejection (n=11), polyomavirus nephropathy (n=3), and other (n=2). A total of 6 patients underwent successful kidney retransplantation so the dialysis-free rate in surviving patients was 87.5%. Overall pancreas graft survival (insulin-free rate) was 65% and the death-censored PTx graft survival rate was 72%. Causes of PTx loss (n=70) included early (n=16) or late (>3 months post-PTx, n=3) thrombosis, death with a functioning PTx (n=18), acute or chronic rejection (n=30), and infection (n=3). A total of 8 patients underwent successful pancreas retransplantation so the insulin-free rate among surviving patients was 80%. In the 30 patients with graft failure from rejection, 4 died, 11 did not have detectable C-peptide, and 15 continued to exhibit C-peptide production and had partial pancreas function although all were insulin-requiring. Using C-peptide production (rather than insulin independence) as the definition of graft survival, the death-censored PTx graft survival rate was 80% and the graft survival rate in surviving patients (including pancreas retransplants) was 88%. Consequently, in patients with severe diabetes, excellent 5 year outcomes following PTx could be achieved as >86% of patients were alive, >87% of surviving patients were dialysis-free, 80% of surviving patients remained insulin-free, and 88% of surviving patients had detectable C-peptide levels.

## Discussion

Our experience with 202 PTxs spanning an 11+ year period is documented herein and chronicles evolving aspects of recipient selection, technical considerations, immunosuppression, and recipient management protocols based on multiple prospective and retrospective studies of our own outcomes. Improving outcomes in vascularized PTx are due to a number of factors including reductions in both technical and immunologic graft losses as well as surgical complications. At our center, surgical technique (portal-enteric drainage preferred), type of transplant (SKPT versus SPT), and transplant number (primary versus retransplantation) do not appear to impact outcomes. Based on our prospective study findings comparing Alem and rATG in SKPT, which demonstrated lower rejection and infection rates in the Alem group, since 2009 we have used single-dose Alem induction (with early steroid elimination) almost exclusively following PTx.[12,14] In 2010, we switched to the ipsilateral technique of SKPT.

Similar to others, we have noted an association between AA ethnicity and type 2 diabetes in the SKPT group19. In our experience, however, AA recipients have a higher rate of

kidney graft loss and dual graft failure but no difference in pancreas graft survival rates compared to non-AA recipients. Our data with PTx in type 2 diabetic patients compares favorably to other reports in the literature and we have confirmed that the decision to perform PTx in diabetic kidney transplant recipients should be based on general acceptance criteria rather than diabetes type.[19,20] Because SKPT is associated with a shorter waiting time, enhanced donor quality, increased life expectancy, higher graft survival, improved quality of life, and better preservation of renal function compared to deceased donor kidney transplantation alone in diabetic patients, characterization of the "type" of diabetes may be irrelevant and insulin-requiring diabetic patients should be evaluated for SKPT based exclusively on their predicted ability to tolerate the surgical procedure (which has a higher inherent complication rate compared to kidney transplantation alone) and requisite immunosuppression as well as comply with a more stringent post-transplant follow-up regimen compared to kidney transplantation alone. However, we noted that PTx in AA recipients was characterized by fewer SPTs and PTxs with portal-enteric drainage, more patients with detectable HLA antibodies and C-peptide levels at the time of PTx, more HLA-mismatching, and more patients with a type 2 diabetes phenotype. Although survival rates and the incidences of early thrombosis and acute rejection were similar, AA patients were at a greater risk for kidney graft loss or dual graft loss compared to non-AA patients in the absence of mortality. This finding may imply either a greater risk for graft loss, better survival in the presence of graft loss, or both, in AA patients.

In our experience, surveillance pancreas biopsies in SPT have revealed a finite incidence of subclinical rejection, allowing for early treatment and optimization of maintenance immunosuppression.[6,18] We have demonstrated equivalent mid-term PTx survival rates in SPT and SKPT and believe that this is related in part to the early diagnosis and treatment of subclinical rejection episodes in combination with careful graft selection and attention to HLA matching in SPT. In spite of the morbidity of PTx and chronic immunosuppression, at 5 years follow-up, at least 80% of surviving patients are dialysis and insulin-free.

## Summary

In the new millennium, a number of evolving trends have occurred in PTx at our center including: 1. Conversion from rATG induction with steroid maintenance to Alem induction with early steroid elimination in the setting of TAC/MMF maintenance immunosuppression; 2. Increasing donor and recipient age; 3. Ipsilateral placement of both organs in SKPT; 4. Biopsy-directed immunosuppression, with liberal use of reperfusion, surveillance, clinically indicated and follow-up biopsies both in SKPT and SPT; 5. Successful transplantation of patients with a "type 2 diabetes" phenotype; and 6. A decrease in the annual number of PTxs being performed in the setting of continued growth in our kidney transplant program. The national trend in decreasing numbers of PTxs being performed in the United States is disturbing and probably related to a number of factors including more stringent donor selection (and fewer ideal donors), increasing donor and recipient obesity, overall improvements in the medical management of diabetes (including better insulin analogues, insulin pumps, and sensor devices), financial concerns, and access issues.[3,21,22]

The goals of PTx include freedom from exogenous insulin, better health and well-being, and improved quality of life and life expectancy. Achieving any of these goals might be a reasonable measure of success. For patients with end stage diabetic nephropathy, annual mortality on the waiting list over the past decade has ranged from 7 to 10%.[23] Given the projection that many recipients will live well into their second decade following transplantation, the outcome of diabetic sequelae and rehabilitative potential may be determined by the severity and reversibility of their disease at the time of transplantation. Although PTx results in euglycemia and insulin independence, these benefits are offset by the potential for surgical complications and the short- and long-term sequelae of chronic immunosuppression, leading to a compression of morbidity. SKPT has become accepted as a preferred alternative to kidney alone transplantation in selected recipients with insulin-requiring diabetes because it is associated with superior glycemic control, improved quality of life, enhanced life expectancy, and is cost-effective. In the future, PTx will remain an important option in the

treatment of "complicated" insulin-requiring diabetes because of its metabolic efficiency until other strategies are developed that can provide equal glycemic control with less or no immunosuppression or less overall morbidity.

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