RANDOMIZED CONTROLLED TRIAL

Pancreas transplantation: The Wake Forest experience in the new millennium

Jeffrey Rogers, Alan C Farney, Giuseppe Orlando, Samy S Iskandar, William Doares, Michael D Gautreaux, Scott Kaczmorski, Amber Reeves-Daniel, Amudha Palanisamy, Robert J Stratta

Jeffrey Rogers, Alan C Farney, Giuseppe Orlando, Michael D Gautreaux, Robert J Stratta, Department of General Surgery, Wake Forest Baptist Medical Center, Winston Salem, NC 27157, United States

Samy S Iskandar, Department of Pathology, Wake Forest Baptist Medical Center, Winston-Salem, NC 27157, United States

William Doares, Scott Kaczmorski, Department of Pharmacy, Wake Forest Baptist Medical Center, Winston-Salem, NC 27157, United States

Amber Reeves-Daniel, Amudha Palanisamy, Department of Internal Medicine (Nephrology), Wake Forest Baptist Medical Center, Winston-Salem, NC 27157, United States

Author contributions: Rogers J, Farney AC, Orlando G and Stratta RJ contributed equally to this work, including study design, data analysis and writing the manuscript; Iskandar SS, Doares W, Gautreaux MD, Kaczmorski S, Reeves-Daniel A and Palanisamy A provided critical review and revisions of the manuscript.

Correspondence to: Robert J Stratta, MD, Department of General Surgery, Wake Forest Baptist Medical Center, Medical Center Blvd., Winston Salem, NC 27157, United States. rstratta@wakehealth.edu

Telephone: +1-336-7160548 Fax: +1-336-7135055

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Abstract

AIM: To investigate the Wake Forest experience with pancreas transplantation in the new millennium with attention to surgical techniques and immunosuppression.

METHODS: A monocentric, retrospective review of outcomes in simultaneous kidney-pancreas transplant (SKPT) and solitary pancreas transplant (SPT) recipients was performed. All patients underwent pancreas transplantation as intent-to-treat with portal venous and enteric exocrine drainage and received depleting antibody induction; maintenance therapy included tapered steroids or early steroid elimination with my-cophenolate and tacrolimus. Recipient selection was based on clinical judgment whether or not the patient exhibited measureable levels of C-peptide.

RESULTS: Over an 11.25 year period, 202 pancreas transplants were performed in 192 patients including 162 SKPTs and 40 SPTs. A total of 186 (92%) were primary and 16 (8%) pancreas retransplants; portal-enteric drainage was performed in 179 cases. A total of 39 pancreas transplants were performed in African American (AA) patients; of the 162 SKPTs, 30 were performed in patients with pretransplant C-peptide levels > 2.0 ng/mL. In addition, from 2005-2008, 46 SKPT patients were enrolled in a prospective study of single dose alemtuzumab *vs* 3-5 doses of rabbit anti-thymocyte globulin induction therapy. With a mean follow-up of 5.7 in SKPT *vs* 7.7 years in SPT recipients, overall patient (86% SKPT *vs* 87% SPT) and kidney (74% SKPT *vs* 80% SPT) graft survival rates as well as insulin-free rates (both 65%) were similar (P = NS). Although mortality rates were nearly identical in SKPT compared to SPT recipients, patterns and timing of death were different as no early mortality occurred in SPT recipients whereas the rates of mortality following SKPT were 4%, 9% and 12%, at 1-, 3- and 5-years follow-up, respectively (P < 0.05). The primary cause of graft loss in SKPT recipients was death with a functioning graft whereas the major cause of graft loss following SPT was acute and chronic rejection. The overall incidence of acute rejection was 29% in SKPT and 27.5% in SPT recipients (P = NS). Lower rates of acute rejection and major infection were evidenced in SKPT patients receiving alemtuzumab induction therapy. Comparable kidney and pancreas graft survival rates were observed in AA and non-AA recipients despite a higher prevalence of a "type 2 diabetes" phenotype in AA. Results comparable to those achieved in insulinopenic diabetics were found in the transplantation of type 2 diabetics with detectable C-peptide levels.

CONCLUSION: In the new millennium, acceptable

medium-term outcomes can be achieved in SKPT and SPTs as nearly 2/3rds of patients are insulin independent following pancreas transplantation.

Core tip: Vascularized pancreas transplantation is able to establish a chronic insulin-free state characterized by normoglycemia. In selected recipients with insulin-requiring diabetes, simultaneous kidney-pancreas transplantation has become acknowledged as a favored alternative to kidney alone transplantation because of more intense glucose control, enhanced quality of life and improved long-term survival. The evolution in surgical technique, current patient management strategies, and biopsy directed immunosuppression have resulted in excellent outcomes, even in populations previously considered high risk, such as African-American recipients, patients with a "type 2 diabetes" phenotype and solitary pancreas transplants recipients.

INTRODUCTION

Although first developed as a modality to re-establish endogenous insulin secretion (C-peptide production) reactive to normal feedback controls, vascularized pancreas transplantation (PTx) has evolved over the past several years to complete β cell replacement that frees the patient both from the need to monitor serum glucose as well as the need to administer insulin in order to control diabetes. Patients who present following a total pancreatectomy for benign disease, or those with type 1 or type 2 diabetes, both of which require the administration of insulin, are appropriate candidates for PTx. In the search for a definitive treatment that restores normal glucose homeostasis in patients with complicated diabetes, and alleviates the risk of severe hypo/hyperglycemia, PTx is currently the only procedure that can accomplish this objective and may avert, stabilize, or reverse progressive diabetic complications.

As of December 2010, the International Pancreas Transplant Registry had received data on > 35000 PTxs whereas the Collaborative Transplant Study database had recorded nearly 9000 cases[1,2]. PTx in diabetic patients is separated into 3 chief categories; those performed following either a successful living or deceased donor kidney transplant [sequential pancreas after kidney (PAK) transplant], those occurring in patients with preserved native renal function [pancreas transplant alone (PTA)], and most commonly, those performed simultaneous with a kidney transplant (SKPT). The former 2 categories are frequently analyzed together as solitary pancreas transplants (SPT) because of similar outcomes. Until 2004, the annual number of PTxs progressively increased in the United States but has since declined, with particular reference to the PAK transplant category[1,3,4]. In the past 10 years, both the number of patients being added to the waiting list and the number of pancreata being recovered from deceased donors have decreased whereas the proportion of recovered pancreata being discarded and time on the waiting list for recipients have increased. In addition, recipient age and body mass index (BMI) have increased for PTx in the past decade concomitant with the proportion of recipients who are either African American (AA) or characterized as having type 2 diabetes[1,3,4].

At present, about 9% of PTxs are PTA, 16% PAK, and the remaining 75% are performed as SKPTs[1,3,4]. Success rates for PTx have progressively improved, secondary to refinements in diagnostic and therapeutic technologies and surgical techniques, advancements in immunosuppression and anti-infective prophylaxes, new and effective techniques in organ retrieval and preservation technology and increased experience in the selection of donors and recipients[1,3-5]. Over time, improvements in outcomes have occurred in all 3 PTx categories as a result of a decrease in technical failures and immunologic graft losses. At present, five-year patient survival rates are 89% in PTA, 87% in SKPT, and 83% in PAK transplant recipients. One-year patient survival is more than 95% in the cases of recipients of primary deceased donor PTxs whereas 10-year patient survival exceeds 70% in all 3 categories[1].

The definition of PTx graft survival is variable but principally defined as absolute freedom from exogenous insulin therapy, concomitant with the absence of atypical glycemic excursions, in contrast to other modalities utilized for the treatment of diabetes. According to Registry data, one-year insulin-free rates are currently 78% in PTA, 80% in PAK, and 85% in SKPT recipients. These data indicate that we may now expect pancreas graft half-lives approaching fourteen years in SKPT and ten years in SPT recipients[1,3-5]. The focus of this study was the retrospective review of PTx outcomes at our center in the emergent millennium.

MATERIALS AND METHODS

Recipient selection

Diabetes mellitus treated with exogenous insulin, the presence of diabetic complications, and the ability to endure the surgical procedure, were significant indications in the selection of candidates for PTx. In addition, there existed the need for these recipients to be predictably

able to manage the requisite immunosuppression and expected follow-up, irrespective of detectable C-peptide levels. The selection criteria for SKPT in type 2 diabetes have been previously reported[6-8]. Selection criteria for SPT were similar to SKPT except for renal function, in which the glomerular filtration rate (GFR), determined by the abbreviated Modification of Diet in Renal Diseases (aMDRD) formula, was > 70 mL/min in PTA (native renal function) and > 40 mL/min in PAK (renal allograft function) transplant recipients already on a calcineurin inhibitor. Donor selection was more stringent for SPT, including younger donors and a minimum of a 2-3 human leukocyte antigen (HLA) match[7,9].

Technical aspects

The history of PTx has been essentially defined by the evolving trends in surgical techniques. We performed our first SKPT at Wake Forest Baptist Health (WFBH) on 6/3/92[7]. The exocrine secretions were managed with bladder drainage using a short donor duodenal segment conduit. Although the patient initially did well with excellent dual allograft function, she ultimately required enteric conversion on 12/20/07 for persistent difficulties related to bladder drainage including dehydration, episodes of gross hematuria requiring blood transfusions, metabolic acidosis and recurrent urinary tract infections. At 22 years follow-up, this pancreas allograft continues to exhibit acceptable function and the patient remains insulin-free. The next PTx at WFBH was not performed until the latter part of 2001.

Since November, 2001, all PTxs were initially approached as intent-to-treat with portal-enteric drainage using an anterior approach to the superior mesenteric vein (SMV). Enteric drainage was performed by side to side duodeno-enterostomy to the recipient's proximal ileum[7,10]. We used diverting Roux limbs infrequently, which were reserved for cases in which the allograft duodenum did not reperfusion well. 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. Relative "contraindications" to portal venous drainage have been previously reported[10]. In patients (particularly male) with a high BMI, the SMV can be quite deep in the mesentery and the donor common iliac artery bifurcation "Y" graft might not be long enough to reach the recipient's iliac artery through a window in the distal ileal mesentery, even with the liberal use of a donor artery "extension" graft. In these cases, systemic venous and enteric drainage were performed to simplify the procedure.

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].

Anti-coagulation

Two thousand to three thousand units of intravenous heparin (30-50 units/kg) were administered to SPT and selected SKPT recipients, as a bolus prior to implantation of the pancreas. Following surgery and in the absence of bleeding, patients received a continuous heparin infusion, starting at 300 units/h on day 1, then 400 units/h on day 2, and then 500 units/h on days 3-5 after which time it was terminated[12]. Indications for intravenous heparin included SPT, preemptive SKPT, prolonged pancreas cold ischemia (> 15 h), small or diseased donor or recipient vessels, history of thrombophilia or clotting disorder in the recipient, history of prior pancreas graft thrombosis or extended donor criteria.

Immunosuppression

From 1/02-12/03, 37 patients received depleting antibody induction therapy with 3-5 doses of rabbit antithymocyte globulin (rATG) (1.5 mg/kg per dose); maintenance therapy consisted of tapered steroids, mycophenolate mofetil (MMF) and tacrolimus (TAC)[13]. Subsequently, 16 patients received multi-dose rATG induction, 4 received alemtuzumab (Alem) and rATG, and 5 patients were administered a single dose Alem (30 mg) at the time of transplant. Six of these patients underwent early steroid elimination during this transitional period.

From early 2005 to late 2008, 46 SKPT recipients were part of a prospective trial conducted at WFBH. This undertaking compared a single 30 mg intra-operative dose of Alem to multi-dose rATG (1.5 mg/kg per dose starting intra-operatively) induction. On alternate days, rATG induction was administered (minimum of 3 doses; total cumulative dose 5-6 mg/kg). Both groups received maintenance therapy with early steroid elimination, half-dose MMF (1 gm/d) initially, and full dose TAC (titrated to 12 h trough levels of 8-12 ng/mL)[14].

After completion of rATG, the dose of MMF was doubled to two gm/day. In patients with gastrointestinal intolerance or myelosuppression, the MMF dose was reduced. Corticosteroids were withdrawn after 5 d 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 patients who receive PTxs at our center (*n* = 74) have been given single dose Alem induction with MMF, TAC, and either rapid prednisone taper (dose reduction to 5 mg/d by 2 mo following PTx if determined to be high immunological risk), or early steroid elimination[15].

Infection prophylaxis

Fluconazole, valganciclovir, and trimethoprim-sulfamethoxazole were administered to all patients as an anti-infective prophylaxis[7,14]. Cephazolin was used as a peri-operative antibiotic prophylaxis according to the following schedule: (1) A single pre-operative dose; (2) An intra-operative dose; and (3) 2-3 post-operative doses (1 g intravenous).

For at least 12 mo, every Monday, Wednesday and Friday, patients received single-strength trimethoprim-sulfamethoxazole 1 tablet as prophylaxis for Pneumocystis jiroveci. Oral fluconazole (50-200 mg/d) served as an anti-fungal prophylaxis for 1-2 mo. Oral valganciclovir 450 mg/d for 3 mo was the drug of choice as an anti-viral prophylaxis. Dosage was adjusted for either leukopenia or renal dysfunction. If the recipient was at risk for primary cytomegalovirus (CMV) exposure (donor CMV seropositive, recipient CMV seronegative), then oral valganciclovir at a daily dose of 900 mg (with adjustments to dosage as above) was given for a period of 6 mo[7,14].

Peri-operative management

All patients received daily anti-platelet therapy with 81 mg of aspirin. For those patients requiring the post-operative placement of a tunneled central venous catheter, or those requiring prolonged vascular access, a low daily dose of oral warfarin (1 mg) was given to reduce the risk of catheter-associated thrombosis. After insertion of a tunneled subclavian venous catheter, the majority of patients were then sent home on a regimen that included oral electrolyte supplementation and intravenous fluids at home, for a time that was individualized for each patient. Patients were followed closely in the Transplant Outpatient Clinic (at least twice weekly) for the first 3 mo post-transplant and other patient health conditions were treated as indicated.

Diagnosis and treatment of rejection

Elevation in the serum creatinine level of > 0.3 mg/dL without obvious cause triggered the diagnosis of renal allograft rejection, which was made by renal allograft biopsy. The Banff classification was used to determine the severity or grade of rejection[16]. In addition to clinically indicated kidney biopsies, both immediate reperfusion and 1 mo protocol have been performed in SKPT recipients since March, 2008; this, unless there was a specific contraindication. Three steroid boluses and/or oral prednisone recycle were used to treat Banff grade Ia renal rejection episodes. For episodes of acute rejection that did not respond (histologically or clinically) to bolus steroid therapy, rATG rescue therapy was used as the next treatment. Antibody-mediated rejection episodes and Banff grades I b and Ⅱ grades of rejection were also treated with rATG with the number of doses based on clinical and biochemical parameters. A one month follow-up biopsy was subsequently performed to confirm improved histopathologic changes. The presence of inflammation either on the 1 mo surveillance (subclinical rejection) or follow-up biopsy (persistent rejection) was usually an indication for additional steroid therapy and a subsequent follow-up biopsy.

An unexplained rise in serum amylase, glucose or lipase levels provided clinical suspicion to the diagnosis of rejection of the pancreas graft. Following percutaneous biopsy of the pancreas, the Maryland Classification System[17] was used, initially in the treatment of rejection. More recently, the Banff 2007 schema was utilized[18]. Most grades of pancreas allograft rejection were treated with rATG, while borderline and mild rejection episodes were treated with steroids. In order to document histological improvement and response to therapeutic intervention, follow-up pancreas allograft biopsies were performed. Until there were 2 consecutive biopsies considered as "normal", following SPT, surveillance pancreas biopsies were performed every 3-4 wk[19]. Biochemical parameters were the determinants for clinical biopsies.

Statistical analysis

Both prospective and retrospective databases provided data for compilation. The chi-square test was applied for when variables were categorical, and, with limited data, Fisher's exact test was used. Continuous data were portrayed as means and standard deviations and categorical data were portrayed as percentages and proportions. Significance was ascribed to a two-tailed *P*-value of < 0.05.

RESULTS

From 11/1/01 through 3/1/13, a total of 202 PTxs were performed in 192 patients, including 40 SPTs and 162 SKPTs. The former category included 5 PTA and 35 PAK transplants. 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 sequentially or simultaneously (one patient received a kidney following a PTA). In addition, 6 patients (3%) underwent subsequent kidney retransplantation. PTx with portal venous and enteric exocrine drainage was performed as intent-to-treat; however, in 23 cases, systemic venous and enteric exocrine drainage was performed (11%) in which portal-enteric drainage was not deemed safe or possible. Indications for systemic-enteric drainage were central obesity (7), difficult vascular anatomy (*n* = 7), and retransplant of the pancreas (*n* = 9), in which the prior PTx was performed with portal venous and enteric exocrine drainage). The incidence of systemic-enteric technique was 7.5% for primary PTxs (*P* < 0.0001) *vs* 56% for pancreas retransplants. The proportion of male recipients (70% *vs* 56%), rate of early relaparotomy (48% *vs* 36%) and recipients ≥ 80 kg (30% *vs* 24%), were all slightly higher in patients undergoing PTx with systemic venous and enteric exocrine drainage. Rates of early PTx thrombosis were 8% in portal-enteric PTxs *vs* 4% in systemic-enteric (*P* = NS). Comparable survival rates were found, with an average follow-up of 4.5 years in systemic-enteric *vs* 5.5 years in portal-enteric

PTx recipients, respective patient survival (87% *vs* 86%), PTx graft survival (78% *vs* 62%, *P* = 0.165) and kidney graft survival (78% *vs* 77%).

Pancreas retransplantation

Of the 16 (8%) pancreas retransplants, indications for retransplantation were early thrombosis following SKPT (*n* = 9) or PAK (*n* = 1), primary PTx loss secondary to rejection (*n* = 4), primary nonfunction (*n* = 1), and recurrent auto-immunity (*n* = 1). Types of pancreas retransplants included PTx following SKPT (*n* = 10), second PAK (*n* = 3), second SKPT (*n* = 2), and second PTA (*n* = 1). Eleven patients underwent allograft pancreatectomy prior to retransplantation and 3 at the time of pancreas retransplantation. There were no instances of early PTx thrombosis in pancreas retransplants compared to an incidence of 8.6% in primary PTxs (*P* = NS). Six patients underwent kidney retransplantation for either early (thrombosis, *n* = 1) or late (chronic allograft nephropathy, *n* = 5, mean 61 mo) graft loss. With a mean follow-up of 72 mo in retransplants *vs* 65 mo in primary PTx, respective patient survival (95% *vs* 86%), PTx graft survival (64% *vs* 65%) and kidney graft survival (82% *vs* 75%) rates were comparable.

Prospective study of alemtuzumab vs rATG induction

In the prospective study of Alem *vs* rATG induction in SKPT, 18 (39%) received rATG induction and 28 patients (61%) received Alem. Enrollment in the two groups was not equal because the randomization schema also included concurrent patients undergoing kidney transplantation alone. Delayed kidney graft function, PRA > 20%, retransplantation, or young AAs (below age 40) were used to identify patients as high immunologic risk, who were managed with chronic steroid therapy (*n* = 11); all other patients were deemed low immunologic risk and underwent early steroid elimination (*n* = 35). Mean follow-up was 5.7 years. With reference to donor, recipient, or transplant characteristics, there were no significant differences between the 2 groups. No differences were noted in one- or five-year patient survival rates. Similarly, one- and five-year uncensored and death-censored kidney and pancreas graft survival rates were comparable. In early PTx thromboses (3.6% Alem *vs* 11% rATG), there were no differences. The same applied to readmissions and other surgical complications between groups. In the Alem group, the overall rates of major infection (39.3% Alem *vs* 66.7% rATG, *P* = 0.13), CMV infection (0 Alem *vs* 16.7% rATG, *P* = 0.054) and acute rejection (21.4% Alem *vs* 44.4% rATG, *P* = 0.11) were slightly lower. In patients with functioning grafts, mean serum creatinine at 1 year (1.1 mg/dL Alem *vs* 1.2 mg/dL rATG) and 5 years (1.4 mg/dL Alem *vs* 1.6 mg/dL rATG), mean calculated aMDRD GFR at 1 year (57 ± 16 mL/min Alem *vs* 55 ± 14 mL/min rATG) and 5 years (55 mL/min Alem *vs* 52 mL/min rATG), glycohemoglobin at 1 year (5.2% Alem *vs* 5.1% rATG) and 5 years (both 5.4%), and mean C-peptide at 5 years (2.2 Alem *vs* 2.3 ng/mL rATG, all *P* = NS) levels were similar in the Alem and rATG groups.

As a result of this study, we switched from rATG to Alem induction therapy in all of our PTx recipients since 2009.

SKPT in AA recipients

Inferior outcomes following kidney transplantation may be a function of AA ethnicity, but data are limited in PTx. From 11/01 to 3/13, a total of 39 PTxs (1 PTA, 2 PAK and 36 SKPT) were carried out in AA recipients and the other 163 in recipients of other ethnicities (1 Hispanic, 1 Asian, and 161 Caucasian).

Donor and recipient demographics are shown in Table 1. The AA group had a longer duration of pretransplant dialysis (mean AA 32 mo *vs* 16 mo other), fewer preemptive transplants (5.5% AA *vs* 28% other), fewer SPTs (8% AA *vs* 23% other), more patients with a current PRA ≥ 10% (28% AA *vs* 10% other), more PTxs performed using the systemic-enteric technique (23% AA *vs* 9% other), more patients with 0-1 HLA matches (64% AA *vs* 42% other), and fewer patients who were CMV seronegative (28% AA *vs* 48% other, all *P* < 0.05). Furthermore, the AA group had more patients with a body weight ≥ 80 kg (51% AA *vs* 24% other), more patients with diabetes for ≤ 18 years (38% AA *vs* 17% other) and more patients with pretransplant C-peptide levels above 2.0 ng/mL (36% AA *vs* 14% other, all *P* < 0.05).

Outcomes are shown in Table 2. Actual patient (90% AA *vs* 86.5% other), kidney (67% AA *vs* 77% other) and pancreas graft survival (59% AA *vs* 66% other, all *P* = NS) rates were comparable with a follow-up mean of 67 mo. Early PTx thrombosis rates (10% *vs* 7%) and early relaparotomy (46% *vs* 36%) were likewise comparable in the AA and other groups, respectively. Between groups, cumulative clinical acute rejection rates were similar (33% AA *vs* 27% other).

In AA patients, death-censored dual graft loss was much higher (22% AA *vs* 6% other, *P* = 0.01). In addition, the death-censored kidney graft survival rate (70% AA *vs* 87% other, *P* = 0.03) was lower in the AA group. In AA patients who were pretransplant C-peptide positive (*n* = 14) *vs* C-peptide negative (*n* = 25), there were no differences in mortality (7% *vs* 12%), kidney graft loss (21% *vs* 36%), or pancreas graft loss (36% *vs* 44%) rates, respectively. Based on this analysis, we concluded that PTx in AA recipients was characterized by a higher frequency of detectable HLA antibodies and C-peptide levels at the time of PTx, less HLA-matching, fewer SPTs and PTxs with portal-enteric drainage, and more patients with a type 2 diabetes phenotype. Although rates of survival, acute rejection and pancreas thrombosis were similar, AA patients were at an increased risk for kidney graft loss or dual graft loss compared to other 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.

Table 1 Donor and recipient characteristics in African-American *vs* non-African-American recipients

	AA *n* = 39	Non-AA *n* = 163[1]	*P* value
Donor age (yr)	24.7 ± 10.2	25.2 ± 9.4	NS
Donor BMI (kg/m²)	23.6 ± 5.4	23.7 ± 2.8	NS
Cold ischemia time (h)	15.8 ± 4.6	16.3 ± 3.8	NS
5-6 HLA-mismatch	25 (64.1%)	68 (41.7%)	0.01
HLA-mismatch	4.8 ± 1.0	4.4 ± 1.2	NS
PRA > 10%	11 (28.2%)	17 (10.4%)	0.008
CMV Recipient negative	11 (28.2%)	78 (47.9%)	0.03
CMV D+/R-	7 (17.9%)	45 (27.6%)	NS
Retransplant	2 (5.1%)	14 (8.6%)	NS
Portal-enteric technique	30 (76.9%)	149 (91.4%)	0.02
SKPT	36 (92.3%)	126 (77.3%)	
SPT	3 (7.7%)	37 (22.7%)	0.04
Recipient age	41.7 ± 9.8	43.0 ± 10.4	NS
Recipient gender: male	20 (51.3%)	94 (57.7%)	NS
Recipient weight ≥ 80 kg	20 (51.3%)	39 (23.9%)	0.001
Recipient weight	70.9 ± 11.9	71.2 ± 12.7	NS
Dialysis history: SKPT hemodialysis	29/36 (80.6%)	54/126 (42.9%)	
Peritoneal dialysis	5/36 (13.9%)	37/126 (29.4%)	
None (preemptive)	2/36 (5.5%)	35/126 (27.8%)	0.004
Duration of dialysis: SKPT (mo)	31.8 ± 15.1	15.6 ± 17.8	0.02
Duration of pretransplant diabetes ≤ 18 yr	15 (38.5%)	27 (16.6%)	0.004
Duration of diabetes (yr)	19.7 ± 8.4	26.9 ± 8.6	0.03
Age of onset of diabetes	20 ± 8	16 ± 6	NS
SKPT waiting time (mo)	11.5 ± 6.4	9.7 ± 7.2	NS
C-peptide positive	14 (35.9%)	16 (9.8%)	0.001

[1]161 Caucasian, 1 Asian, 1 Hispanic ethnicity. AA: African-American; BMI: Body mass index; HLA: Human leukocyte antigen; CMV: Cytomegalovirus; PRA: Panel reactive antibody; SKPT: Simultaneous kidney-pancreas transplantation; SPT: Solitary pancreas transplantation; NS: Not significant.

Table 2 Outcomes in African-American *vs* non-African-American recipients

	AA *n* = 39	Non-AA *n* = 163[1]	*P* value
Patient survival	35 (89.7%)	141 (86.5%)	NS
Death with functioning grafts	1 (2.6%)	14 (8.6%)	NS
Kidney graft survival	26 (66.7%)	123/159 (77.4%)	NS
Death-censored kidney graft survival	26/37 (70%)	123/143 (87%)	0.03
Pancreas graft survival	23 (59%)	108 (66.3%)	NS
Death-censored pancreas graft survival	23/37 (62%)	108/148 (73%)	NS
Death-censored dual graft loss	8/37 (21.6%)	9/142 (6.3%)	0.01
Follow-up (mo)	64.9 ± 38.2	69.8 ± 28.6	NS
Relaparotomy	18 (46.2%)	58 (35.6%)	NS
Early thrombosis	4 (10.3%)	12 (7.4%)	NS
Acute rejection	13 (33.3%)	44 (27.0%)	NS

[1]161 Caucasian, 1 Asian, 1 Hispanic ethnicity. AA: African-American; NS: Not significant.

SKPT in "type 2 diabetes"

Over an 11+ year period, we performed 162 SKPTs including 132 in patients with absent or low C-peptide levels (< 2.0 ng/mL, including 21 with measurable C-peptide) and 30 in patients with C-peptide levels ≥ 2.0 ng/mL (mean C-peptide level 5.7 ng/mL, range 2.1-12.4). At the time of SKPT, patients who were C-peptide positive had a later age of onset of diabetes mellitus (mean age 34 years C-peptide positive *vs* 16 years C-peptide negative, *P* = 0.0001), weighed more (mean 77 C-peptide positive *vs* 69 kg C-peptide negative, *P* = 0.27), had a higher proportion that were age 50 years or older (40% C-peptide positive *vs* 23% C-peptide negative, *P* = 0.06), and had more AAs (47% C-peptide positive *vs* 17% C-peptide negative, *P* = 0.001) compared to those with no or low C-peptide levels. In C-peptide positive patients, diabetes duration was shorter (mean 17 years C-peptide positive *vs* 25 years C-peptide negative, *P* = 0.01) but duration of dialysis was performed over a longer period (median 40 mo C-peptide positive *vs* 14 mo C-peptide negative, *P* = 0.14). The 2 groups did not vary according to dialysis modality or history, sensitization, matching, or

Table 3 Donor and recipient characteristics according to pancreas transplantation category

	SKPT *n* = 162 in 161 patients[1]	SPT *n* = 40 in 38 patients[1]	*P* value
Donor age (yr)	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 (h)	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 (yr)	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: AA	36 (22.2%)	3 (7.9%)	0.03
Recipient weight (kg)	71.1 ± 13.5	70.7 ± 12.8	NS
Dialysis history: hemodialysis	82 (50.9%)	NA	
Peritoneal dialysis	42 (26.1%)		
None (preemptive)	37 (23.0%)		
Duration of pretransplant diabetes (yr)	25.3 ± 9.8	26.7 ± 7.7	NS
Waiting time (mo)	10.1 ± 6.3	5.8 ± 7.2	0.002

[1]One patient had 2 SKPTs, two had 2 SPTs, and seven had SKPT followed by SPT. AA: African-American; HLA: Human leukocyte antigen; CMV: Cytomegalovirus; PRA: Panel reactive antibody; SKPT: Simultaneous kidney-pancreas transplantation; SPT: Solitary pancreas transplantation; NS: Not significant; NA: Not available; BMI: Body mass index.

other significant variables.

With a mean follow-up of 5.5 years, patient survival (85% C-peptide negative *vs* 87% C-peptide positive), kidney graft survival (72% C-peptide negative *vs* 77% C-peptide positive), and pancreas graft survival (66% C-peptide negative *vs* 57% C-peptide positive, all *P* = NS) rates were comparable between groups. Death-censored kidney [both 85% and pancreas (77% C-peptide negative *vs* 61% C-peptide positive, both *P* = NS)] rates of graft survival were similar between groups. In each group, death-censored dual graft loss occurred in 11%. Rates of early relaparotomy (36% *vs* 33%) and thrombosis (9.8% *vs* 3%) were the same in C-peptide negative and positive groups, respectively. In follow-up, at the five-year point, there were no differences in surgical complications, major infections, HbA1c and C-peptide levels, acute rejection episodes (29% *vs* 30%), readmissions, or renal functional parameters among the 2 groups.

With these findings in mind, C-peptide positive diabetic patients undergoing SKPT appear to have a phenotype consistent with type 2 diabetes (more frequently AA, obese, older, longer duration of pre-transplant dialysis and later age of onset and shorter duration of diabetes) compared to insulin deficient patients at the time of SKPT. However, survival outcomes were comparable. As a result, pretransplant C-peptide levels, provided that they are < 10 ng/mL, are not used solely by us to identify appropriate patients for SKPT.

SKPT vs SPT
We compared outcomes in 162 SKPT and 40 SPT recipients. Demographic characteristics for SKPT *vs* SPT were, in the majority, comparable (Table 3); notwith-standing this, the SPT group had less HLA mismatching (SKPT mean 4.5 ± 1.2 *vs* SPT 2.7 ± 1.5), younger donors (SKPT mean 27 ± 11 years *vs* SPT 22 ± 7.6 years), a lower incidence of AA recipients (SKPT 22% *vs* SPT 8%), shorter waiting time (SKPT mean 10 mo *vs* SPT 6 mo) and an increased number of retransplants (SKPT 1.2% *vs* SPT 35%, all *P* < 0.05). Outcomes are shown in Table 4. With a mean follow-up of 5.7 years *vs* 7.7 years (*P* = NS), overall patient (86% SKPT *vs* 87% SPT), kidney (74% SKPT *vs* 80% SPT) and pancreas graft survival (both 65%) rates were comparable.

Mortality was nearly equivalent following either SKPT (13.6%) or SPT (13.2%). No differences in mortality occurred when comparing primary (13.6%) *vs* pancreas retransplants (6.25%, *P* = NS). However, patterns and timing of death were different as no early mortality occurred in SPT recipients whereas the rates of mortality following SKPT were 4%, 9% and 12%, at 1-, 3- and 5-years follow-up, respectively (*P* < 0.05). In SPT patients who died, none experienced death with both grafts functioning (DWBGF; 4 had previous kidney graft and 3 previous pancreas graft loss) whereas 15/21 (71%) SKPT recipients experienced DWBGF. In the 26 patients who died, 15 died while both grafts were still functioning, 6 died following pancreas failure, 3 died following kidney graft failure, and 2 died following asynchronous kidney and pancreas graft failure. Secondary to technical issues, 3 SKPT patients died early (within 5 mo) of infection. The remaining 23 deaths occurred at a mean of 53 mo post-transplant (range 6-90). Major causes of late deaths were 7 infectious, 11 cardiovascular, 2 malignancy, and 3 from miscellaneous causes (1 motor vehicle wreck, 1 drug overdose, 1 dialysis withdrawal). Patients aged 50

Table 4 Outcomes according to pancreas transplantation category

	SKPT n = 162 in 161 patients[1]	SPT n = 40 in 38 patients[1]	*P* value
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 (mo)	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 yr post-transplant	10 (6.2%)	0	NS
Death with functioning grafts	15 (9.3%)	0	0.007

[1]One patient had 2 SKPTs, two had 2 SPTs, and seven had SKPT followed by SPT. SKPT: Simultaneous kidney-pancreas transplantation; SPT: Solitary pancreas transplantation; NS: Not significant.

and older at the time of PTx comprised 42% of those who subsequently died compared to 23% of survivors (*P* = 0.05).

Pancreas graft loss was most commonly associated with death (with a functioning graft), (DWFG) in SKPT recipients whereas acute and chronic rejection accounted for the majority of pancreas graft failures in SPT recipients. Rates of early thrombosis were 8.6% in SKPT and 5% in SPT patients. The overall incidence of clinically evident, pancreas acute or biopsy proven kidney rejection in SKPT was similar to the incidence of clinically evident, biopsy proven pancreas rejection in SPT (SKPT 29% *vs* SPT 27.5%, *P* = NS). As a result of this experience, we concluded that in the setting of careful donor and recipient selection, HLA matching, antibody induction with either rATG or Alem, portal-enteric drainage, flow cytometry crossmatch testing, peri-operative anticoagulation, PTx biopsy monitoring, and TAC/MMF maintenance immunosuppression, similar results can be achieved in SKPT and SPTs.

Experience with allograft pancreatectomy
Of the 202 PTxs, 70 PTx graft losses occurred, of which 21 (30%) resulted in allograft pancreatectomy. Allograft pancreatectomy was performed in 10% of patients; indications were early thrombosis (*n* = 16), late thrombosis (*n* = 2), rejection (*n* = 1), infection (*n* = 1), and pancreatitis/uncontrolled leak (*n* = 1). The incidence of allograft pancreatectomy was 12.5% in pancreas retransplants compared to 10% in primary PTxs. In addition, the incidence was 13% with systemic-enteric drainage compared to 10% with portal-enteric drainage. With a mean follow-up of 70 mo in patients with allograft pancreatectomy compared to 65 mo in PTx recipients without allograft pancreatectomy, respective patient survival (81% *vs* 87%) and kidney graft survival (67% *vs* 76%) rates were comparable. In summary, allograft pancreatectomy was performed in 30% of PTx graft losses, was usually related to early graft loss secondary to thrombosis, and did not appear to impact medium-term patient or kidney graft survival rates.

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 5.5 years being the mean follow-up, 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.

Censored kidney graft survival was 84% and uncensored (actual) was 75%. Reasons for kidney graft failure (*n* = 49) included chronic allograft nephropathy (*n* = 12), DWFG (*n* = 21), polyomavirus nephropathy (*n* = 3), acute/chronic rejection (*n* = 11), and other (*n* = 2). Six patients underwent successful kidney retransplantation, therefore leaving a dialysis-free rate of 87.5% in those patients who survived.

Censored PTx graft survival was 72% and uncensored (actual, insulin-free) was 65%. Reasons for PTx failure (*n* = 70) included acute or chronic rejection (*n* = 30), death with a functioning PTx (*n* = 18), early (*n* = 16) or late (> 3 mo post-PTx, *n* = 3) thrombosis, and infection (*n* = 3). The insulin-free rate among surviving patients was 80%, in view of the fact that a total of 8 patients underwent successful pancreas retransplantation. Among the 30 patients with rejection-based graft failure, 11 were without measureable C-peptide, 4 died, and 15 continued to have measureable C-peptide and had limited pancreas function notwithstanding the fact that all were insulin-requiring. Using the detection of C-peptide for graft survival, the success rate in surviving patients (including pancreas retransplants) was 88% and the death-censored PTx graft survival rate was 80%.

As a result, in patients with severe diabetes, excellent 5 year outcomes following PTx were achieved, as > 86% of patients were still alive, > 87% of survivors were dialysis-free, 88% of survivors had detectable C-peptide levels, and 80% of patients who survived remained insulin-free.

DISCUSSION
The Wake Forest PTx experience in the new millennium is documented herein and chronicles evolving aspects of

recipient selection, technical considerations, immunosuppression, and recipient management protocols based upon numerous 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. Even with antibody induction and contemporary immunosuppression, when compared to SKPT, SPT is associated with lower pancreas graft survival rates, and higher rates of acute rejection and immunologic pancreas graft loss[1,3-5]. Urinary amylase and serum creatinine levels are unavailable for the diagnosis of rejection in SPTs with enteric exocrine drainage. Moreover, monitoring pancreatic enzymes (lipase and amylase) may not always be reliable. Because of the difficulties in detecting SPT rejection, we advocate protocol pancreas biopsies in these patients[7,19].

Others have reported the value of performing surveillance biopsies of the pancreas allograft as a form of immunologic monitoring[20]. However, in spite of efforts to detect solitary pancreas allograft rejection in a timely fashion, acute rejection episodes occurring late (> 1 year after transplant) are more common in SPT compared to SKPT. Furthermore, the presence of acute rejection and SPT are the two most important risk factors for pancreas graft loss secondary to chronic rejection[21]. We believe that the use of Alem induction coupled with surveillance pancreas biopsy monitoring are reasons why we are able to achieve similar mid-term outcomes in SPT and SKPT[7]. Our data and the experience of others suggests the safety and efficacy of Alem induction in either SKPT or SPT[14,22,23].

A number of recent reports, including our own, have demonstrated the safety and efficacy of SKPT in patients with a type 2 diabetes phenotype[6,7,24,25]. In one series, 94% of recipients of PTxs that were technically successful became completely insulin-free[24]. Long-term results, in type 1 diabetic PTx recipients, were comparable in this study. Ten and twenty year outcomes have been reported by Light *et al*[25,26] from the Washington Hospital Center in either type 1 or type 2 diabetic patients undergoing SKPT. These groups were defined by the presence or absence of C-peptide, respectively. In keeping with our experience, the type 2 diabetic patients were older at the onset of diabetes, had a higher BMI, and contained a higher AA proportion. No differences, similar to our experience, were identified in long-term outcomes in these studies, suggesting that the presence of C-peptide or "type" of diabetes are not important factors in determining recipient selection for SKPT.

We present herein data on 202 PTxs performed at WFBH in the past 11+ years. During this time, we have chronicled a number of changes including: (1) Switching to single dose Alem induction with early withdrawal of corticosteroids in combination with chronic immunotherapy with TAC and MMF dual therapy; (2) Advancing age both in donors and recipients; (3) Transplantation of both the pancreas and kidney on the right side; (4) Immu-nosuppressive management based on histologic findings with planned implementation of immediate reperfusion kidney biopsies, scheduled pancreas biopsies, as well as clinically indicated and follow-up biopsies; (5) Better understanding of the role of SKPT in patients with a "type 2 diabetes" phenotype; and (6) Reduction in the volume of PTxs in spite of increases in the number of kidney transplants being performed.

Fewer PTxs being performed is not unique to our program but reflects a national trend. There are probably a number of reasons why PTx activity has decreased over time including more restrictive donor selection (and fewer ideal donors), increasing prevalence of obesity among donors and recipients, a number of advances in the medical treatment of diabetes (including new insulin analogues, more sophisticated insulin pumps and glucose sensor devices, better identification and follow-up), financial constraints, and difficulties with access to the waiting list[27,28]. In spite of these drawbacks, whole organ PTx provides an auto-regulating endogenous source of insulin that is able to achieve euglycemia long-term, which in essence renders the patient "ex-diabetic". 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%[29]. Although PTx results in an insulin-free normoglycemic state, these benefits are offset by the potential for surgical complications and the short- and long-term sequelae of chronic immunotherapy, which results in a compression of morbidity. In the future, PTx will remain a useful therapeutic intervention for "complicated" insulin-requiring diabetes because of its metabolic efficiency. Because islet transplant success is defined by C-peptide production and absence of hypoglycemia rather than freedom from insulin therapy and usually involves > 1 donor pancreas, future comparisons of PTx *vs* islet transplant should incorporate similar definitions of graft failure, measures of success, and emphasize longer-term outcomes.

COMMENTS

Background
Vascularized pancreas transplantation (PTx) provides a self-regulating internal source of C-peptide that is consistently able to achieve an insulin-free condition with euglycemia. PTx in diabetic patients is performed in 3 major settings; either before (pancreas transplant alone), after (pancreas after kidney), or concurrent with a kidney transplant (simultaneous kidney-pancreas transplant). The goals of PTx include freedom from exogenous insulin therapy, better health and well-being, and improved quality of life and life expectancy without the need for close glucose monitoring.

Research frontiers
Important areas of research in PTx include targeted or individualized immunosuppression, development of better immune and graft monitoring, improving the donor organ supply, and gaining insights into the pathophysiology of rejection as well as all types of diabetes that result in specific microvascular and metabolic complications.

Innovations and breakthroughs

Success rates for PTx have progressively improved in the past 4 decades, secondary to refinements in diagnostic and therapeutic technologies, improvements in surgical aspects, advancements in therapeutic immunosuppression and anti-infective prevention, new and effective techniques in organ retrieval and preservation technology and increased experience in the selection of donors and recipients. The history of PTx has closely paralleled advances in immunosuppression and surgical techniques.

Applications

In the future, PTx will remain an effective therapy for "complicated" insulin-requiring diabetes because of its metabolic efficiency until new treatments are developed that can achieve normoglycemia without either immunotherapy or major morbidity.

Peer review

Excellent descriptive manuscript of pancreas and kidney transplants.

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