Evolution of Native Kidney Function After Pancreas Transplantation Alone

H. Le Dinh, A. DeRoover, C. Coimbra, L. Weekers, J. Léonet, M. Meurisse, and J.P. Squifflet

ABSTRACT

Introduction. This study investigated changes in kidney function over time among a cohort of patients undergoing pancreas transplantation alone (PTA) from January 2002 to December 2011.

Patients and Methods. Ten of eighteen PTA patients bearing functioning grafts for at least 1 year were recruited for the analysis. Primary endpoints were changes in mean serum creatinine (SCr, mg/L) and mean estimated glomerular filtration rate (eGFR) using the 4-variable Levey-MDRD equation (mL/min/1.73 m²) comparing baseline (pretransplantation) to 6-month, 1-year, 3-year, and 5-year posttransplantation values. Mean follow-up time was 75.7 ± 20.5 months (range, 46–106.5).

Results. Baseline eGFR was 89.3 ± 27.9 (range, 58–145). eGFR decreased to 75.7 ± 26.2, 71 ± 20.6, 66.5 ± 14.8, and 62.1 ± 11.2 at 6 months, 1, 3, and 5 years representing −15.2%, −20.5%, −15.8%, and −22.6% percentage decreases respectively (P < .05 for all pairwise comparisons). The Baseline SCr was 8.6 ± 2.3 mg/L (range, 5–13). SCr progressively increased to 10.1 ± 3, 10.5 ± 3.1, 10.9 ± 3.1, and 11.3 ± 1.7 at 6 months, 1, 3, and 5 years a 17.1%, 22%, 16.6%, and 19.9% increase respectively (P < .05 for all pairwise comparisons). One of ten, 2/8, and 3/7 patients displayed an eGFR <60 at transplantation versus 3 and 5 years thereafter, respectively. No patient developed a SCr > 25 mg/L or eGFR <30 or needed dialysis or kidney transplantation. Five of ten patients had micro-albuminuria or proteinuria before transplantation. Tacrolimus levels were within recommended therapeutic ranges over time.

Conclusion. Kidney function deteriorated significantly after PTA. Understanding of risk factors for the development of renal impairment is important to preserve kidney function and to select appropriate candidates for PTA.

Pancreas transplantation alone (PTA) enables patients to be insulin-independent with normalized glucose metabolism, thereby halting or reversing early diabetic nephropathy. However, it is a challenging technique with a high incidence of surgical complications together with an elevated risk of immunologic responses. Additionally the nephrotoxic effects of life-long immunosuppressive therapy on native kidney function posttransplantation could counterbalance the late beneficial impacts of glycemic control. Thus, compared with other types of pancreas transplantation, only a small proportion of cases are PTA. Few studies of the natural history of kidney function have been performed among diabetic populations undergoing beta-cell replacement by either islet transplantation or PTA. The understanding of risk factors for the decline in native kidney function appears to be vital to preserve kidney function and to select appropriate candidates for transplantation. This study sought to examine changes in kidney function over time among a cohort of PTA to evaluate
potential recipient risk factors related to a progressive decline in kidney function posttransplantation.

PATIENTS AND METHODS
We performed a retrospective study of 18 PTA and 28 simultaneous pancreas and kidney (SPK) transplantations performed in 15 and 25 patients, respectively from January 2002 to December 2011. Ten PTA patients with functioning pancreas grafts for at least 1 year were recruited for the analysis. All patients displayed brittle insulin-dependent diabetes mellitus (IDDM) with frequent hyperglycemic episodes and hypoglycemic unawareness, coma and/or seizures, and/or inability to function without help. Indications for PTA included type-1 IDDM (n = 9) and de novo diabetes after hepatic transplantation (n = 1). The average follow-up was 75.7 ± 20.5 months (range, 46–106.5).

Transplant Procedure
In all cases, the pancreas was recovered from a brain-dead donor as part of a multi-organ procurement. After flushing it was cold-stored in University of Wisconsin solution. Mean donor age was 29.2 ± 13.6 years (range, 15–56), all of them were male. Mean donor body mass index (BMI) was 23.7 ± 2.7 kg/m² (range, 19.4–29.4). Mean cold ischemia and suture times were 478 ± 193 (range, 152–694) and 31 ± 3.2 minutes (range, 24–35), respectively. A common aortic patch carrying the celiac trunk and the superior mesenteric artery (SMAP) was present in 8 grafts, whereas an arterial reconstruction with a donor iliac artery Y graft was necessary in 2 cases. Portal vein extension was required for 3 grafts. An arterial reconstruction with a donor iliac artery Y graft was superior mesenteric artery (SMA) was present in 8 grafts, whereas an arterial reconstruction with a donor iliac artery Y graft was necessary in 2 cases. Portal vein extension was required for 3 grafts.

Mean recipient ages at the time of transplantation and of IDDM diagnosis were 36 ± 9.6 (range, 21–55) and 15.7 ± 14.3 years (range, 3–51), respectively. Mean duration of IDDM was 20.4 ± 12.1 years (range, 3–40). The male/female ratio was 3/7. Mean recipient BMI was 25 ± 2.9 kg/m² (range, 21.4–30.1). Mean HLA mismatches were 3 ± 1.2 (range, 0–4). The transplantation was a primary graft (n = 8) or a retransplantation (n = 2). Transplantation was performed trans-peritonally through a midline incision with the pancreas graft placed fully in a retroperitoneal location in the right iliac fossa. To manage exocrine secretions, duodenocystostomy, duodenojunostomy, or duodeno-duodenostomy were constructed in 2, 5, and 3 cases, respectively. We tended to perform a duodenoduodenostomy technique for PTA due to the advantage to monitor the graft duodenum via upper endoscopy. The donor portal vein was Anastomosed end-to-side to a major tributary of the recipient superior mesenteric vein (n = 6) or end-to-side to the recipient external iliac vein (n = 4). The arterial anastomosis was usually constructed in end-to-side fashion between the donor iliac artery Y graft (or the common aortic patch of celiac trunk and SMA) and the recipient common iliac artery.

Perioperative and Postoperative Management
Induction therapy consisted of either a lymphocyte-depleting agent (thymoglobulin or rATG) or an anti-CD25 monoclonal antibody (basiliximab); maintenance therapy combined 3 immunosuppressive drugs-tacrolimus, mycophenolate mofetil or mycophenolic acid, and steroids. Tacrolimus was adjusted to achieve whole blood trough levels of 10–15 ng/mL during the first 3 months posttransplantation, 7–10 ng/mL from month 3 to month 12, and 5–7 ng/mL thereafter. Steroids (methylprednisone) were progressively tapered to attain 4 mg/d by 3 months and completely withdrawn from month 6. Anti-infective prophylaxis comprised Tazocin (piperacillin and tazobactam) in association with Diflucan (fluconazole) for the first 5 days, sulfamethoxazole/trimethoprim for pneumocystis and urinary tract infection for at least 6–12 months, and valganciclovir for cytomegalovirus (CMV) depending on donor and recipient CMV serological status (if D+/R−: valganciclovir for 3 months; other cases: acyclovir for herpes virus for 3 months). The pancreas grafts were monitored with serum amylase and lipase, urinary amylase (if the pancreas exocrine gland was drained into the bladder), blood glucose, and HbA1c (glycosylated hemoglobin A1c). Abdominal scan with contrast injection to assess the graft perfusion was routinely performed at day 5 posttransplantation when there was any suspicion of technical complications. A protocol duodenal biopsy was applied at 3 and 8 weeks posttransplantation followed by every 3 months for the first year and yearly afterward in cases of PTA with duodeno-duodenal drainage. Otherwise in the presence of any of the following signs—hyperamylasemia, hyperlipasemia, unexplained hyperglycemia, fever, or graft tenderness—suspected pancreas rejection was treated empirically.

Study Design and Statistical Analysis
Serum creatinine (Scr, mg/L) and eGFR, which was calculated via the 4-variable Levey-Modification of Diet in Renal Disease (MDRD) equation (mL/min/1.73 m²) were used to evaluate renal function. We compared the mean changes in Scr and eGFR from baseline (pretransplantation) to 6 months, 1 year as well as 3 and 5 years posttransplantation.

Continuous variables were expressed as mean values ± standard deviation (SD), categorical variables were expressed as proportions or percentage. Intragroup comparisons were performed using paired Student t tests for continuous parameters. Graft and patient survival rates estimated using the Kaplan-Meier method were and compared using the log-rank test. P < .05 was considered to be statistically significant. All data were analyzed using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS
Eight PTA grafts were excluded from this analysis due to early graft thrombosis on day 1, day 2, or day 60 posttransplantation (n = 3), late graft thrombosis at 7.5 months (n = 1), rejection at months 3 and 4 (n = 2), and functioning for less than 1 year (n = 2). In these cases, the drainage technique consisted of systemic-venous (n = 1), systemic-duodenal (n = 1), systemic-enteric (n = 3), and portal-duodenal (n = 3).

Cohort of 10 PTA Transplants
Baseline SCr level of 8.6 ± 2.3 mg/L (range, 5–13) progressively increased to 10.4 ± 3.5 at 3 months (P = .01), 10.1 ± 3 at 6 months (P = .00), 10.5 ± 3.1 at 1 year (P = .03), 10.9 ± 3.1 at 3 years (P = .02), and 11.3 ± 1.7 at 5 years (P = .02). The percentage increase in SCr was 21.5%, 17.1%, 17.5%, 22%, 16.6%, and 19.9% at these times. Baseline eGFR of 89.3 ± 27.9 mL/min (range, 58–145) decreased to 74 ± 26.8 (P = .00), 75.7 ± 26.2 (P = .00), 71 ± 20.6 (P = .04), 66.5 ± 14.8 (P = .02), and 62.1 ± 11.2 (P = .01) at 3 and 6 months as well as 1, 3, and 5 years, respectively. The mean absolute decrease in eGFR was −15.3, −13.6, −18.3, −12.5, and −18.2 mL/min at the corresponding time which translated
NATIVE KIDNEY FUNCTION

Table 1. Glyco-metabolic Profile in PTA

<table>
<thead>
<tr>
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<th>Pre-transplant</th>
<th>3 months</th>
<th>6 months</th>
<th>1 year</th>
<th>3 years</th>
<th>5 years</th>
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<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>-</td>
<td>91.4 ± 15.8 (72-116)</td>
<td>91.9 ± 16.1 (70-121)</td>
<td>91.2 ± 16.9 (70-122)</td>
<td>93.5 ± 14.9 (75-119)</td>
<td>99 ± 7 (85-107)</td>
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<td>HbA1c (%)</td>
<td>8.9 ± 1.2 (7.4-11)</td>
<td>5.7 ± 0.4 (4.9-6.2)</td>
<td>5.5 ± 0.6 (4.1-6.3)</td>
<td>5.7 ± 0.4 (5.1-6.5)</td>
<td>5.7 ± 0.3 (5.2-6.1)</td>
<td>5.6 ± 0.3 (5.2-6.2)</td>
</tr>
<tr>
<td>C-peptide (pmol/mL)</td>
<td>0.03 ± 0.02 (0.5-1.7)</td>
<td>1.2 ± 0.4 (0.9-2.9)</td>
<td>1.5 ± 0.6 (0.4-2.2)</td>
<td>1.2 ± 0.7 (0.4-2.1)</td>
<td>1.3 ± 0.5 (0.6-1.7)</td>
<td>1.2 ± 0.4 (0.6-1.7)</td>
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Pretransplant plasma glucose levels fluctuated in a wide range and were not collected.
displayed an eGFR <30 mL/min or required renal replacement therapy. Gruessner et al reported 2% or 12% of PTA recipients to develop kidney failure, as defined by the need for dialysis or kidney transplantation at 1 or 5 years after transplantation in the tacrolimus era. The corresponding numbers in the cyclosporine era were 5% and 13%. In total, 15% of PTA patients under a calcineurin inhibitor (CNI) regimen develop kidney failure at 5 years. An impact of PTA on the decreased kidney function was demonstrated by both direct measurement of GFR and calculation methods, which have generally shown a good correlation.

Various factors seemed to have been involved in the impaired renal function post-PTA. Recipient age younger than 30 years and SCr >15 mg/L at the time of pancreas transplantation were associated with kidney failure in PTA recipients using a multivariate analysis. An eGFR <60 or 70 mL/min prior to transplantation was also linked to a greater likelihood of progression to clinically significant kidney disease. Albuminuria or proteinuria prior to transplantation, which reflect the underlying subclinical diabetic nephropathy may predispose the native kidney to injury posttransplantation. Polyoma virus arising from the native kidneys may also contribute to the rapid evolution of renal dysfunction in PTA patients despite an adequate eGFR at the time of transplantation.

Solitary pancreas grafts are particularly susceptible to acute rejection, but there are no reliable laboratory or clinical findings for early detection of these episodes except a strict protocol of pancreas biopsies. With accumulated experience in bladder- and enteric-drained pancreas transplantation since 2007, we modified our management of the pancreas exocrine gland by draining it into the recipient duodenum. This technique prefers the advantage of easy monitoring of the graft by upper endoscopy of the duodenum. Moreover, duodenal findings on duodenum biopsies paralleled those of pancreatic tissue biopsies. Among 7 acute rejection episodes occurring among the cohort of 10 PTA cases 4 were detected by the surveillance biopsy. Gruessner el al reported a higher propensity for native kidney failure among patients who underwent treatment for more than 2 rejection episodes.

Due to their nephrotoxic side effects CNI remain the principle culprit for deterioration of renal function. However, current attempts to avoid CNI altogether have not been successful. Future studies are necessary to determine whether the incidence of kidney dysfunction can be reduced by fine-tuning existing PTA protocols. The immunological advantage of portal venous drainage with a low rate of rejection may also permit reduction in immunosuppressive therapy with improved long-term outcomes.

Our outcomes of SPK cohort were similar to our previously reported results and comparable to those noted by other authors. The PTA cohort, however, displayed a lower pancreas graft survival than that usually cited in the literature. Graft losses were mostly due to vascular graft thrombosis occurring early or late posttransplantation. Explanations for the frequency of thrombosis may include the recipient’s vascular status, the pancreas’s low flow rate, and the vascular reconstruction using an extension graft. Our observation has led us to preferentially avoid this reconstruction, asking the liver procurement team to leave the

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**Fig 1.** Overall pancreas graft survival in the cohorts of PTA and SPK. Three-month, 1-, 3- and 5-year survival rates were 76.6%, 57.4%, 51.1%, and 51.1% in PTA cohort, and 85.7%, 82.1%, 82.1%, and 72.7% in SPK cohort, respectively.

**Fig 2.** Overall patient survival in the cohorts of PTA and SPK. Three-month, 1-, 3- and 5-year survival rates were 100%, 100%, 93.3% and 93.3% in PTA cohort, and 92.9%, 92.9%, 92.9% and 88.2% in SPK cohort, respectively.
pancreatic vessels with the celiac trunk and SMA en bloc on an aortic patch.\textsuperscript{16}

In conclusion, native kidney function deteriorated significantly after PTA.

REFERENCES


