Living related donor pancreas and pancreas-kidney transplantation

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Our experience with living related donor (LRD) pancreas transplants shows that they can be performed with low morbidity and mortality for both donors and recipients. The recipient survival rate is 90% at both 1 and 5 years post-transplant. Our overall pancreas graft survival rate is comparable to that for cadaver transplants; if only technically successful cases are included, the graft survival rate is significantly better for LRD (versus cadaver) transplants. Advantages for LRD recipients include fewer rejection episodes, less immunosuppression, lower incidence of graft loss from rejection, and elimination of waiting time. Donor mortality in our series was 0%, and the incidence of surgical complications about 10–15%. LRD pancreas transplants are an attractive option for endocrine replacement therapy in certain diabetic patients. Optimal candidates are: (i) patients who are highly sensitized and have a low probability of receiving a cadaver graft; (ii) patients who should avoid high-dose immunosuppression; (iii) patients with nondiabetic identical twins; and (iv) uremic patients who want one operation with no waiting in order to remain or become dialysis free as well as insulin-independent. These transplants can be performed safely in all recipient categories — pancreas transplant alone, pancreas after kidney or simultaneous pancreas-kidney transplant. In all groups, LRD transplants should be done only when the donor, the recipient, and the entire family understands the advantages and disadvantages of LRD versus cadaver transplants.

The success with living related donors (LRDs) for kidney transplantation has led to their use for other solid organs. The pancreas was the first extrarenal organ to successfully use LRDs. Over the last 5 years, LRDs have been used in liver, lung, and intestinal transplants. LRD transplants offer several advantages (versus cadaver transplants), including elimination of waiting time, decreased cold ischemic injury, improved immunological matching, and overall improved graft survival. Use of LRDs also expands the donor pool, which is important for organs such as kidney and liver, where there is a shortage of cadaver organs. However, the number of pancreas transplants currently being performed is less than the number of cadaver organs available; if matching is ignored, there is no shortage of pancreases at present. The main advantages of LRD pancreas transplants (versus cadaver transplants) are...
a lower incidence of rejection episodes, higher graft survival rates\(^2\), and elimination of waiting time. Rejection has been a major problem after cadaver pancreas transplants, particularly when done without a kidney, accounting for up to 30% of graft loss within the first year\(^3\); the corresponding number after LRD transplants is significantly lower\(^4\). With new immunosuppressants, the cadaver organ rejection rate is now low\(^3\), giving less incentive for a solitary LRD pancreas transplant than before, but a shortage of cadaver pancreases for all who could benefit remains as incentive for the LRD approach.

This immunological and logistical advantage must be weighed against the higher technical failure rate seen with LRD (versus cadaver) pancreas transplants. Only a segment of the pancreas is transplanted, and the vessels used for engraftment (splenic artery and vein) are shorter and smaller in diameter. Thus, LRD pancreas grafts are more prone to arterial and venous thrombosis than their cadaver counterparts. Nonetheless, the technical failure rate after LRD pancreas transplants has been lower than the immunological failure rate (i.e. graft loss from rejection) after cadaver solitary pancreas transplants\(^6\). Therefore, for technically successful pancreas transplants, the probability of long-term success is significantly better with an LRD (versus a cadaver) allograft. Another advantage of LRD transplants is that they may be the only option for highly sensitized patients and for those requiring minimal immunosuppression.

LRD pancreas transplants may be done either for nonuremic patients (PTA, pancreas transplant alone) or for patients who have received a previous kidney transplant (PAK, pancreas after kidney). Another option for uremic patients with insulin-dependent diabetes mellitus (IDDM) is a simultaneous pancreas–kidney transplant (SPK). Compared with a sequential transplant (PAK), an SPK transplant requires only one procedure, and the physical consequences are no different for the donor. For uremic diabetic patients who want only one operation and want to avoid or minimize time on dialysis, a LRD SPK transplant is particularly attractive.

**Donor evaluation**

LRD transplants have the potential for harm to the donor. Thus, it is crucial that all potential donors undergo a thorough pre-operative evaluation. The purpose is two-fold: first, to ensure that the donor is healthy enough to undergo the operation safely; and, second, to ensure that the reduced pancreatic mass would be sufficient to maintain a normal metabolic state.
The general health of the donor is best ascertained by a detailed history and physical examination, looking for evidence of cardiovascular, pulmonary, renal, and major gastrointestinal disease. This part of the workup is no different from the evaluation for any other general surgical patient undergoing a pancreatic resection.

Endocrinological evaluation includes family history. Potential donors should be at least 10 years older than the age of onset of diabetes in the recipient (and the onset of diabetes in the recipient must have been at least 10 years pretransplant). In addition, for sibling donors, no family member other than the recipient should be diabetic. When these two criteria are met, donors are at no greater risk for diabetes than the general population, even if they are HLA-identical with the recipient. Potential donors should be asked about their alcohol intake. Female donors who have had previous pregnancies should be asked about gestational diabetes.

Metabolic studies must include measurement of the hemoglobin A1c (should be <6%) and an oral glucose tolerance test (OGTT). Plasma glucose is determined in response to a 75 g oral glucose load. Using criteria outlined by the National Diabetes Data Group, potential donors must be excluded if fasting glucose levels are >110 mg/dl (6 mmol/l), if glucose at 2 h post-ingestion measures >140 mg/dl (7.7 mmol/l), or if any glucose value between 1 and 120 min is >200 mg/dl (11 mmol/l). If these studies are normal, insulin secretion should be evaluated in response to an intravenous glucose tolerance test (IVGTT). This test is performed by administering 20 g glucose (as D50W) intravenously (i.v.) and obtaining samples for glucose and insulin levels over a 30 min period after the injection of glucose. Only individuals with post-i.v. glucose stimulatory first-phase insulin levels above the 30th percentile of the normal range should be accepted as donors.

Lastly, some radiological assessment of the vascular anatomy should be done. This step is more important if the kidney is to be procured also, as the vascular anatomy of the splenic artery is fairly constant in comparison to the renal arteries. An aortogram may be done, but more recently, we have been using a noninvasive magnetic resonance angiogram (MRA) study. It will demonstrate any anatomical abnormalities of the pancreas as well as the vascular anatomy of the celiac trunk and renal vessels. In our last 20 SPK donors, MRA has documented normal anatomy of the celiac and superior mesenteric arteries and normal size and location of the splenic artery.

At our center, between January 1, 1978 and March 15, 1997, a total of 103 LRD pancreas transplants have been done (51 PTA, 32 PAK, and 20 SPK). Of the 103 donors, only 3 have not remained normoglycemic (2 at 1 year, 1 at 4 years). All 3 had a normal OGTT, but they donated before routine use of IVGTT; in retrospect, all 3 had low insulin
Transplantation responses. None of the donors meeting the current criteria of the IVGTT insulin response have become significantly hyperglycemic after hemipancreatectomy, though 3 have developed mild elevations of their hemoglobin A1c levels.

Operative techniques

Donor

Pancreas procurement may be done through a subcostal or midline abdominal incision. For SPK donors, a midline incision is preferred. If the kidney is to be removed, it is generally removed first. The right or left kidney can be used, depending on the vascular anatomy. Initially our preference was to procure the right kidney (a somewhat easier dissection); we now prefer to use the left kidney (because of concurrent partial mobilization of the pancreas, greater length of the renal vein, and lack of liver mobilization). The colon on the appropriate side is reflected medially; on the left side, the lienocolic ligament should be preserved, if possible: it may carry collateral blood vessels to the spleen. The kidney can then be dissected from the surrounding perirenal fat. Once the vessels have been dissected free, heparin (70 units/kg) is given and the kidney removed. The heparin effect can then be reversed with protamine (1 cc/1000 units of heparin) before the pancreas is mobilized.

Procurement of the distal pancreas begins with dividing the gastroduodenal ligament laterally to the inferior margin of the spleen (Fig. 1A). Care should be taken to preserve the gastroepiploic artery and the short gastric vessels, to diminish the likelihood of devascularizing of the spleen. The retroperitoneal attachments of the spleen are not disturbed, and the spleen is not mobilized. The stomach can then be retracted superiorly, and the inferior margin of the distal pancreas is mobilized. A peritoneal incision is made over the tail of the pancreas at its junction with the spleen. The pancreas is gently dissected off the splenic surface. The splenic vessels are then identified, and the main trunks of both the splenic artery and vein divided proximal to the splenic branches (again, preserving collateral blood vessels supplying the spleen).

The superior margin of the pancreas is then mobilized, retaining the splenic artery and vein in continuity with the body and tail of the pancreas. As the pancreas is elevated from its bed and retracted medially, the confluence of the inferior mesenteric vein (IMV) as it joins the splenic vein can be seen. The location of this confluence varies; it can be very close to the junction of the superior mesenteric vein (SMV) and the
Fig. 1  (A) Technique of distal pancreatectomy in living related donor for segmental transplantation: from Sutherland et al. (B) Segmental pancreas removed with preservation of donor spleen: from Sutherland et al.
splenic vein. Once the IMV is divided, the pancreas can be mobilized further to the surgical neck.

The portal vein is identified at the confluence of the SMV and splenic vein. The avascular plane between the pancreas and portal vein is bluntly dissected to define the narrowest portion of the pancreas (i.e. the neck). At this site, the pancreas is divided. The splenic artery is then isolated at its origin off the celiac trunk. The pancreatic neck can then be divided using multiple 4.0 silk ligatures. Both ends of the pancreatic duct should be identified. The proximal end can be oversewn, and the distal duct tacked with 7.0 Prolene sutures for identification. The cut edge of the proximal pancreas can be oversewn with interrupted sutures in a U-type fashion to ‘fishmouth’ the proximal cut edge and to decrease the likelihood of pancreatic fluid leaking from the smaller ducts.

At this point, the segmental pancreas graft is ready for removal (Fig. 1B). The donor is again heparinized (70 units/kg), the splenic artery and vein divided, and the pancreas removed (Fig. 1B). Protamine is again given to reverse the heparin effect. The graft is then flushed ex vivo via the splenic artery with University of Wisconsin (UW) solution (about 20 cc) and briefly stored at 4°C in UW before implantation. Before closure, the viability of the spleen must be carefully assessed. If there is bleeding from the spleen, or if it does not appear viable, it should be removed.

**Recipient**

The recipient operation is not very different from its cadaver counterpart. A lower abdominal midline incision is used. If a kidney graft is to be implanted, it should be placed on the left side. The pancreas graft should be placed on the right side if possible, because of the more superficial location of the vessels on this side. In preparation for the pancreas graft implantation, all branches of the iliac vein, including the hypogastric, should be divided (allowing the vein to lie in a more superficial location). To allow for a better alignment, we have often found it useful to divide the internal iliac artery. Doing so gives a better lie to the graft after it is implanted and decreases the chances of the graft artery kinking. The donor splenic artery can then be anastomosed end to side to the external or common iliac artery; the splenic vein is anastomosed end to side to the iliac vein.

Pancreatic exocrine secretions can be managed by a number of techniques. If the pancreatic duct is of adequate size, a direct anastomosis between the duct and bladder mucosa can be constructed with interrupted 7.0 absorbable sutures (Fig. 2A,B). If the duct is small
and the diameter of the cut edge of the pancreas is small, then an invagination technique can be used. The pancreas graft is invaginated into the bladder using one internal layer of 4.0 absorbable sutures and one external layer of interrupted 4.0 nonabsorbable sutures. Doing so obviates the need for a tedious duct-to-mucosa anastomosis, but it could create problems from exposure of exocrine pancreas tissue to urine.

The duct may also be injected with a liquid, such as silicone, that polymerizes rapidly. This obviates the need for, and complications of, an anastomosis to the recipient bladder or bowel. The exocrine pancreas undergoes fibrosis, but the endocrine pancreas remains intact. One drawback with this technique is the inability to monitor exocrine function (through urine amylase levels) as a marker of rejection.

The pancreatic duct may also be drained enterally, using a Roux-en-Y limb of distal bowel (Fig. 3). As with duct injection, one drawback is the inability to monitor exocrine function as a marker of rejection. Therefore, our current preference is bladder drainage with a direct anastomosis between the pancreatic duct and the bladder mucosa if
possible, which allows monitoring of pancreas exocrine secretions in the urine. This is particularly important in solitary pancreas transplants, less so in SPK where the creatinine level can be used as a marker for kidney rejection. Isolated rejection episodes of the pancreas do occur in SPK recipients, but are rare.

Postoperative care

Donor

Postoperative care of donors is not unlike that of any other patient undergoing a major abdominal procedure. A nasogastric tube should be left in place and removed when bowel function returns. Serial hemoglobin determinations are made to monitor for bleeding. Blood sugar and amylase levels are checked routinely. A persistent elevation of the serum amylase level may suggest pancreatitis, a leak, or pseudocyst formation. If pain over the splenic bed persists or is severe, a splenic radionuclide scan should be obtained to ensure viability of the spleen.
If the scan suggests infarction of the spleen, a splenectomy should be done. Donors can usually be discharged home within 1 week.

Recipient

The initial care of LRD recipients is similar to that of cadaver recipients. Plasma glucose levels are determined regularly, and insulin is administered as needed to keep blood sugar levels 150 mg/dl during the first 14 days post-transplant. Intravenous fluids are given according to the central venous pressure and urine output. A nasogastric tube should be left in place until postoperative ileus resolves, usually between post-operative days (POD) 5 and 7.

Given the higher incidence of thrombosis of LRD grafts, some form of coagulation prophylaxis should be instituted. We now systemically heparinize all LRD recipients. Generally, heparin is started intraoperatively at 200 units/h, with full heparinization achieved by 4–6 h postoperatively. On POD 5, Coumadin is started and maintained for 6 months (target INR = 2). Thereafter, recipients take low-dose acetylsalicylic acid (80 mg/day) indefinitely. With this aggressive anticoagulation regimen, we have seen a significant decrease in the incidence of graft thrombosis, but no serious bleeding complications.

Immunosuppression

With our current immunosuppressive protocol, all but HLA-identical recipients receive anti-thymocyte globulin (ATG, 10 mg/kg i.v.) for 5–10 days. Tacrolimus is used as the mainstay immunosuppressive agent. A dose of 2 mg orally twice per day is started on POD 1 or when the serum creatinine level is <3.0 mg/dl. The dose is then adjusted to achieve levels of 8–12 ng/ml during the first month and 5–10 ng/ml thereafter. Prednisone (2 mg/kg/day) is started intra-operatively, then tapered to 0.6 mg/kg/day by 1 week post-transplant, and 0.1 mg/kg/day by 1 month post-transplant. Once recipients are able to tolerate oral intake, mycophenolate mofetil (MMF) is started at 1.5 g twice per day. Before oral intake, azathioprine is used at 1.25 mg/kg i.v. Patients tolerating both MMF and tacrolimus (or cyclosporine) at 6 months are withdrawn from prednisone.
Complications

Donor

Potential complications for donors include bleeding, splenic infarct or abscess, pancreatitis, pseudocyst, and intra-abdominal abscess formation.

Intra-operative bleeding may be encountered with the dissection of the tail of the pancreas from the hilum of the spleen. Operative trauma to the spleen resulting in capsular tears may result in significant bleeding and require splenectomy. Postoperative bleeding from the cut surface of the pancreas is also a potential hazard. Procurement of the kidney can increase the potential sources of bleeding. Of our 20 SPK donors, 4 (20%) required a blood transfusion peri-operatively.

Besides operative trauma, the spleen may also need to be removed if blood supply to it is insufficient after ligation of the splenic vessels. If the spleen infarcts postoperatively, the recipient will have pain over the splenic region, radiating to the left shoulder. Areas of infarct may later develop an abscess. If a radionucleotide spleen scan shows persistent lack of uptake in a recipient with persistent pain, a splenectomy should be done.

Pancreatitis of the residual head and body of the gland is generally not a problem. Pancreatic leakage may occur, either from the main duct or, more commonly, from the small pancreatic duct branches. Of our 103 donors, 1 required a relaparatomy to re-ligate the cut surface of the pancreas after a staple closure. Smaller leaks may later form a pseudocyst, which may become infected. Generally, pseudocysts can be treated successfully with CT-guided percutaneous drainage. Of our 103 donors, 8 developed symptomatic peripancreatic fluid collections postoperatively. Of these, 7 were successfully treated with percutaneous drainage, while 1 required an open drainage procedure.

As with any abdominal procedure, other complications can occur, such as small bowel obstruction secondary to adhesions.

A serious complication for donors is the development of diabetes mellitus. In our series, 3 donors have developed mild diabetes controlled with oral hypoglycemics. Another 3 donors have had elevated postoperative hemoglobin A1c, though none of them have required oral hypoglycemics. Diabetes can be avoided by adhering to the strict preoperative endocrine evaluation outlined previously. Moreover, we now exclude obese (body mass index > 27 kg/m^2) donors, older (age > 45 years) donors, and donors with a history of gestational diabetes or significant alcohol intake. Intra-operatively, we remove no more than half of the gland (i.e. we divide it at the neck, just anterior to the portal vein). Postoperatively, all donors must undergo annual follow-up testing.
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involving OGTT and measurement of hemoglobin A1c levels, to allow long-term assessment of outcome.

Recipient

Postoperative complications for LRD recipients are similar to those seen for cadaver recipients—bleeding, thrombosis, pancreatitis, infections and rejection. The relative frequency of these complications, however, differs.

The incidence of thrombosis is significantly higher with the segmental LRD grafts (versus the whole-organ cadaver)\(^9\). Of our 103 LRD pancreas grafts, 19 (18.5%) were lost because of vascular thrombosis. LRD grafts are at higher risk for thrombosis because the splenic artery and vein allow for less flexibility (compared with the Y-graft used for cadaver grafts); also, they are more prone to bending or twisting. With whole-organ cadaver grafts, there is a dual blood supply (splenic and superior mesenteric arteries); segmental grafts depend on a single vessel (splenic artery). Therefore, partial or complete thrombosis would be more detrimental in a segmental graft. Since instituting our aggressive anticoagulation regimen, we have seen a dramatic decline in graft loss secondary to thrombosis. Another important step to prevent thrombosis is proper alignment of the recipient vessels, with the recipient external iliac artery lying lateral to the vein. We frequently divide the internal iliac artery to allow more flexibility and to avoid impingement of the external iliac artery on the splenic vein\(^10\).

Other reasons for graft loss at early post-transplant include deep infections and graft pancreatitis. The incidence of infection is generally lower with segmental LRD grafts (versus whole-organ cadaver grafts); perhaps related to the absence of duodenum, with its potential for leakage and contamination with enteric flora. Only 2 LRD recipients in our series have lost their graft because of pancreatitis.

Rejection is a less common problem after LRD transplants (versus cadaver transplants). Over an 18 year period, only 13% of our LRD allograft recipients lost their grafts because of chronic rejection versus 41% of our cadaver recipients\(^11\). In our last 20 LRD SPK recipients, only 8 had rejection episodes; only 1 lost the pancreas graft to rejection. All 20 kidneys are functioning and all of the LRD SPK recipients are alive. Even excluding HLA-identical transplants, the incidence of rejection is lower after LRD (versus cadaver) transplants. The newer immunosuppressive drugs (tacrolimus, MMF) may also be contributing to the lower incidence.
Results

Our mortality rate for donors has been 0%. Nor have we seen any recipient deaths directly attributable to the operative procedure. Donor outcome, however, must also take into account surgical complications and metabolic changes postdonation. In our series, the overall incidence of serious surgical donor complications requiring re-operation or radiological interventions was 10–15%. If strict selection criteria are met, the complication of insulin insufficiency in donors can be avoided. Only 3 of our donors developed mild diabetes requiring oral hypoglycemics; all 3 donated before routine use of IVGTT in our pre-operative evaluation.

A quality of life questionnaire was distributed to our 20 SPK donors. Of the 16 who responded, 15 stated they had made the correct decision to donate.

Our pancreas graft survival rate at 1 year was 75%; patient survival, 90%. In the subgroup of 20 SPK recipients, patient survival at 1 year was 100%; pancreas graft survival, 78% and kidney graft survival, 100%12. Currently, all 20 kidney grafts and 15 of the pancreas grafts are functioning. A quality of life survey was also distributed to these 20 recipients. Of the 14 who responded, all 14 stated they made the correct decision to undergo the transplant; all 14 reported an improvement in their health compared with 1 year pretransplant.

References

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