

PANCREAS TRANSPLANTATION FROM LIVING DONORS

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Summary

The pancreas was the first extrarenal organ that was successfully transplanted using a living donor. Since 1979, about 200 living donor pancreas transplants have been performed worldwide. Pancreas transplants from living donors have been done in all 3 recipient categories: initially solitary transplants only (PTA, PAK) and, since 1994, in combination with a living donor kidney (SPK). SPK transplants from living donors were the first living donor dual organ transplants of any kind.

From the *donor* perspective, the surgical principles of distal pancreatectomy for the purpose of living donor pancreas transplantation include preservation of blood supply via the splenic vessels, gentle parenchymal dissection, and preservation of the spleen. The (distal) pancreas was also the first extra-renal solid organ that was successfully procured from a living donor using the minimally invasive (laparoscopic) technique. Living pancreas donors must undergo thorough metabolic testing pre-donation to minimize the risk of developing diabetes post-donation. Strict exclusion criteria have been developed and reduced the rate of post-donation diabetes. No living donor deaths have been reported for distal donor pancreatectomy.

From the *recipient* perspective, advantages of living (vs. deceased) donor pancreas transplantation include elimination of waiting time, shorter preservation time, and, in case of a biological donor, better HLA matching, lower immunologic risk, and less immunosuppression. Living donor grafts are preferentially implanted intraabdominally on the right side using enteric (or bladder) drainage for pancreatic exocrine secretions and systemic venous drainage. Improvements in immunosuppressive and anticoagulatory protocols have resulted in 1-year graft survival rates of > 85% for living donor pancreas recipients. The field of living donor pancreas transplantation has fundamentally contributed to our understanding of Type 1 diabetes: recurrence of autoimmune disease with selective beta cell destruction and isletitis was diagnosed first in living donor grafts of identical twins.

Living donor pancreas transplants are an option if the recipient (1) is highly sensitized (PRA > 80%) and has a low probability of receiving a deceased donor graft; (2) must avoid high-dose immunosuppression; (3) has a nondiabetic identical twin or a 6-antigen-matched sibling; (4) and wants to preempt dialysis (if uremic). Pancreas transplants using living donors can be done safely and successfully in selected donors and recipients.

Key words: pancreas transplantation from living donor, living donor pancreas transplantation laparoscopic distal pancreatectomy, identical-twin pancreas transplants, endocrinological donor work-up, recurrence of disease, bladder drainage, enteric drainage, systemic venous drainage

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INTRODUCTION

Use of a living donor has immunologic advantages, is associated with shorter ischemia times and eliminates waiting time ¹. The vast majority of living donor transplants are kidneys (about 95%) due to their paired organ status ¹. Although the pancreas was the first extra-renal organ that was transplanted successfully ¹⁻⁴, only about 200 pancreas transplants from living donors have been performed worldwide ⁵. In Western countries, the number of pancreas transplants from living donors has steadily declined in the absence of a shortage of deceased pancreas donors. In Asian countries, living donor pancreas transplants have been performed in increasing numbers due to a general shortage of deceased donors ^{5,6}.

Starting in the late 1970s the first pancreas transplants from living donors were performed as solitary transplants (pancreas after kidney transplant [PAK] in 1979 and pancreas transplant alone [PTA] in 1980) ². It was not until 1994, due to concern of the magnitude of the procedure, that a simultaneous pancreas and kidney transplant (SPK) was successfully performed ⁷.

RATIONALE

The rationale for pancreas transplants from living donors has shifted over time.

Initially, in the azathioprine (AZA) and cyclosporin A (CSA) eras, living pancreas donors were used because of better graft survival (as compared with deceased donors).

With the introduction of tacrolimus (TAC) and mycophenolate mofetil (MMF) and their combined use starting in the mid 1990s ^{4,5,8,9}, graft survival improved markedly for deceased donor pancreas recipients, because of a significantly lower graft loss rate from rejection: the immunologic advantage of living donor pancreas transplants in the TAC era was no longer as distinct as it had been in the AZA and CSA eras. For that reason, even though living donor pancreas transplants in the TAC era have a lower graft loss rate from vascular thrombosis (because of vigorous anticoagulation protocols), the incentive for using living donors has waned. Further, in contrast to kidney and liver transplants, a shortage of deceased donors for solitary pancreas transplants does not exist. Thus, in the TAC era, living donors for solitary pancreas transplants are now used only if the recipient (1) is highly sensitized (panel-reactive antibody [PRA] > 80%) and has a low probability of receiving a deceased donor graft; (2) must avoid high-dose immunosuppression; or (3) has a nondiabetic identical twin or a 6-antigen-matched sibling.

THE DONOR

Work-up and endocrinological testing

The principles for evaluating and accepting a potential pancreas donor are not different than for other solid-organ transplants ^{3,10}. The potential donor must understand the nature of the procedure and the risks to his or her health, must not be coerced, must provide voluntary consent, must be mentally competent, and must be of legal age. All potential donors must undergo a thorough medical and psychosocial evaluation. Initial screening usually rules out volunteers with major health problems, e.g., current or previous disorders of the pancreas, active infections or malignancies, major personality disorders, and drug or alcohol dependence. Single parents of minor children are also not considered donor candidates. The social and psychological evaluations assess the donor's voluntarism and altruism as well as the dynamics of the donor-recipient relationship ^{3,10,11}.

The medical evaluation of potential pancreas donors includes both pancreas-nonspecific and -specific tests. The former are the same as for kidney donation and include ABO blood and tissue typing, leukocyte crossmatch and PRA tests, general laboratory tests, etc. Potential donors must also fulfil certain criteria specific to their pancreatic endocrine function as it may relate to post-donation development of diabetes mellitus. Related donors must be at least 10 years older than the age at which the intended recipient was diagnosed with diabetes mellitus. It has been shown that if diabetes is going to develop in a sibling or any other family member who is HLA-identical or matched at the HLA-DR3 or DR4 locus with the recipient, it does so within 10 years of the onset of diabetes in the recipient ^{10,11}. The crucial part of the donor evaluation is the metabolic assessment. However, it must be emphasized that even with sophisticated metabolic testing it is impossible to determine with absolute certainty whether a potential donor will retain normal glucose tolerance after surgery.

The metabolic testing performed in the evaluation process of potential pancreas donors is detailed in Table I. It includes a comprehensive insulin secretory test in the fasting state which measures both arginine- and glucose-induced insulin secretion under basal conditions. Functional beta cell reserve is then measured by the glucose potentiation of arginine induced insulin secretion test (GPAIS) in which the arginine stimulation test is repeated after glucose has been administered intravenously at a rate of 900 mg/min for 60 minutes. A normal response should be greater than 300% of the basal ^{10,11}. Exclusion criteria for living pancreas donation are listed in Table II. Once the potential donor has cleared all medical tests, the donor still needs to undergo a radiographic study to determine the anatomic suitability of the pancreas. Magnetic resonance imaging (MRI) and angiography (MRA)

Table I. Metabolic testing for living donor pancreas candidates* (from Gruessner, Seaquist, 2023; Seaquist, Gruessner, 2008, mod.)^{10,11}.

Fasting glucose level (post 10- to 16-hour fast)
Hemoglobin A1c level
Oral glucose tolerance test (OGTT)
A > 150 g carbohydrate diet is given for 3 days prior to the test and usual physical activity. After a 10- to 16-hour fast (water is permitted, smoking is not), a 75-g oral glucose load in 250–300 ml of water is given over 10 minutes. The end of the drink time is time 0. Measurement of glucose and insulin is performed at the following intervals: -10, -5, 0, 15, 30, 60, 90, 120, 150, 180, 240, and 300 minutes
Arginine stimulation test (AST)
A > 150 g carbohydrate diet is given for 3 days prior to the test and usual physical activity. After a 10- to 16-hour fasting period (water is permitted, smoking is not), the test is commenced between 0730 and 1000 hrs., 5 g of arginine (arginine HCl 10%) via IV push is given over 30 seconds. Time 0 is at the end of the bolus. Measurement of glucose, insulin, glucagon, and C-peptide is performed at the following intervals: -10, -5, 0, 2, 3, 4, 5, 7, 10, 25, and 30 minutes. AIR to arginine is defined as the mean of the peak 3 insulin values between 2 and 5 min following the arginine injection with the basal value subtracted
Intravenous glucose tolerance test (IVGTT)
35 min after the arginine injection, 209m glucose is given IV over 30 seconds. The end of the infusion is time 0. Glucose, insulin, glucagon, and C-peptide are measured at the following intervals: -5, 0, 1, 3, 4, 5, 10, 15, 20, 25, and 30 minutes.
Acute insulin response (AIR) to glucose is defined as the mean of the 3-, 4-, and 5-minute insulin values following the glucose injection with the basal value subtracted. Glucose disposal rate (kg) is defined as the slope of the natural log of glucose values between 10 and 30 min after injection. First-phase insulin release (FPIR) is defined as the sum of insulin levels at 1 and 3 min
Glucose potentiation of arginine-induced insulin secretion (GPAIS)
145 minutes after the last blood draw in the above test, a glucose infusion (D20W) at 900 mg/min is started through an IV pump. The infusion is maintained for 70 minutes. At minute 60, 5 g of arginine (10% arginine HCL) IV is given over 30 seconds. The end of the bolus is time 0. Measurement of glucose, insulin, glucagon, and C-peptide is performed at the following intervals: -10, 0, 2, 3, 4, 5, 7, and 10 minutes. Acute insulin response at 900 mg/min glucose potentiation (AIR-900) is defined as the mean of the 3 peak insulin values between 2 and 5 min with the basal value subtracted
Insulin autoantibodies (IAAS)
Measured by fluid-phase radioassay incorporating competition with cold insulin and precipitation with polyethylene glycol
GAD 65 autoantibodies (GAAS)
Measured in triplicate by radio-assay, using in vitro transcribed and translated recombinant human GAD (65-kDa isoform) and precipitation with protein A-sepharose.
Islet cell antigen 512 autoantibodies (IC512)
ICA512 is measured by radio immunoassay in duplicate using a 96-well plate format with a recombinant ICA512 protein.

have replaced standard angiography because of their less invasive nature.

The anatomy of the splenic artery itself and its blood supply to the tail of the pancreas is quite complex. It can be subdivided into 3 pancreatic segments: suprapancreatic (above the superior margin of the pancreas), retropancreatic (posterior to the superior margin of the pancreatic tail), and prepancreatic (anterior to the tail). The splenic artery gives rise to several intrapancreatic (parenchymal) branches³:

- the dorsal pancreatic artery (DPA) derives close (1–2 cm) to the origin of the splenic artery from the celiac trunk; the DPA passes downwards, dorsal to the neck/body and divides into right and left branches (the right branch supplies part of the head of the pancreas and connects with the pancreaticoduodenal arcades; the left branch becomes the transverse [or inferior] pancreatic artery, runs along the inferior pancreatic border and connects with other intrapancreatic vessels off the splenic artery);

- the great pancreatic artery ("pancreatic magna"), the largest of 2–10 pancreatic branches all of which originate distally of the DPA origin from the splenic artery; it also supplies the pancreatic duct in the tail;
- the caudal pancreatic artery which usually originates from the inferior branch of the splenic artery in the hilum of the spleen; it runs inferiorly and back into the pancreas, connects with the transverse pancreatic artery and is rarely preserved in pancreas procurements from living donors.

Donor distal pancreatectomy

Procurement of the distal pancreas from a living donor using open, laparoscopic or robotic techniques have been described in detail elsewhere^{3,12–15}. The introduction of laparoscopic (hand-assisted) distal pancreatectomy has shortened hospitalization and recovery time with an aesthetically pleasing result, thus making living pancreas donation more attractive (Figs. 1–5)^{13,14}.

Table II. Exclusion criteria for living pancreas donors (from Gruessner, Seaquist, 2023; Seaquist, Gruessner, 2008, mod.)^{10,11}.

Historical and clinical criteria
History of type 2 diabetes in any first-degree relative (parent, sibling, child)
Personal history of gestational diabetes
Additional first-degree relative with type 1 diabetes (other than proposed recipient)
Body mass index greater than 27 kg/m ²
Age greater than 50 years
Age of the donor within 10 years of the age at which type 1 diabetes was diagnosed in the proposed recipient
Clinical evidence of diseases associated with insulin resistance (eg, polycystic ovarian syndrome, hypertension)
Personal history of an autoimmune endocrine disorder involving the thyroid, adrenal, pituitary, gonads
History of or active diseases of the exocrine pancreas (eg, active or chronic pancreatitis)
Active or uncontrolled psychiatric disorders
Heavy smoking, alcoholism, or excessive alcohol use
Hypertension, cardiac disease
Active infections or malignant disorders
Metabolic criteria
Any glucose value above 150 mg/dL during standard oral glucose tolerance tests
Hemoglobin A1c greater than 6%
Glucose disposal rate calculated from data collected during intravenous glucose tolerance tests less than 1.0%
Presence of elevated titer of islet cell autoantibodies or anti-GAD antibodies
Acute insulin response to intravenous glucose or intravenous arginine of less than 300% of basal
Glucose potentiation of arginine-induced insulin secretion of less than 300% of basal

Irrespective of the type of surgical technique (open, laparoscopic or robotic) the following principles of the operation were developed to achieve best outcome^{3,16}:

- manipulation of the gland must be minimized to avoid “surgeon-induced” pancreatitis in both donor and the recipient. This is in contrast to distal pancreatic resections as performed for reasons not related to donation for transplantation (Figs. 2-3);
- the blood supply via the splenic artery and splenic vein must be preserved until shortly before removal of the pancreatic tail. This is in contrast to a distal pancreatectomy for pancreatic cancer where the blood supply may be taken at an early stage (Figs. 2-3);
- spleen preservation is preferred. Spleen preservation as part of a distal pancreatectomy originated from the early living donor pancreas experience by Sutherland¹⁷ which preceded the modification (with or without preservation of the splenic vessels) by Warshaw et al.¹⁸ for benign and malignant pancreatic disorders. Spleen preservation according to the “Sutherland” technique is possible if the (right) gastroepiploic and short gastric vessels can be left intact (Fig. 1);
- meticulous closure of the fishmouth-shaped stump after suture ligation of the distal pancreatic duct should be performed with a running suture (Fig. 4).

After complete dissection of the pancreas, heparin (70 U/kg) is given intravenously. Once the distal pancreas is removed, protamine sulfate is used to reverse the heparin

effect. The distal pancreas is stored at 4°C in UW solution before implantation and flushed under low pressure ex situ via the splenic artery with approximately 20-50 mL UW solution on the back table.

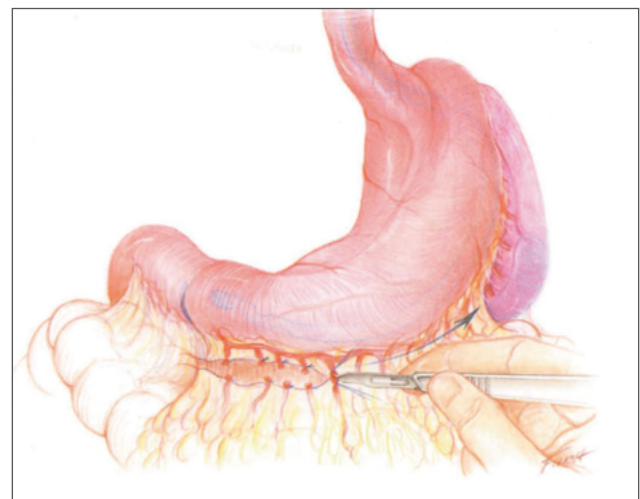


Figure 1. Open distal pancreatectomy (living donor): division of the gastrocolic ligament with preservation of the right gastroepiploic artery (the left gastroepiploic artery arises from the splenic artery which stays with the donor distal pancreas). The branches of the right gastroepiploic artery continue to provide arterial supply to the spleen even after ligation of the distal splenic artery (from Gruessner 2023, mod.)³.

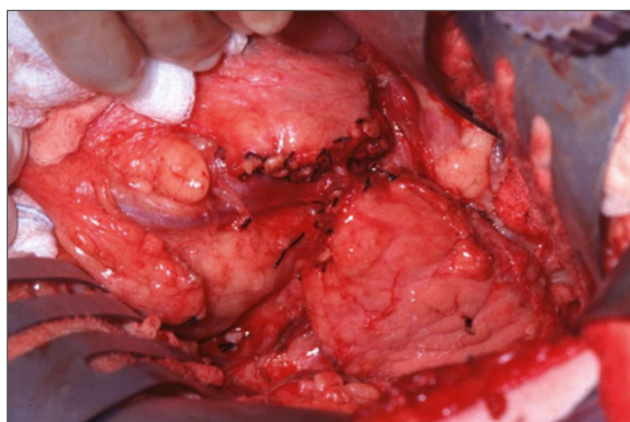


Figure 2. The pancreatic parenchyma is divided between ligatures of 4-0 or 3-0 absorbable sutures. The pancreatic duct is identified (it is usually located slightly superior and posterior to the middle of the pancreas). Once the duct is identified, it is divided with a scalpel and its proximal end is oversewn with 5-0 or 6-0 nonabsorbable sutures (from Gruessner 2023, mod.)³.

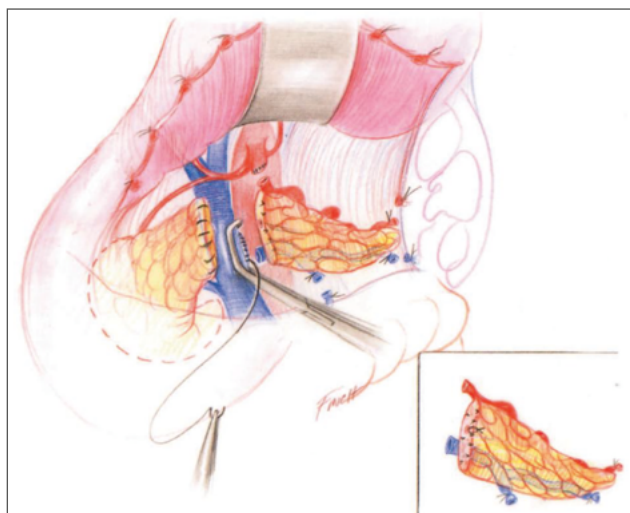


Figure 3. Open distal pancreatectomy (living donor): removal of the distal pancreas. The proximal stump of the splenic artery is oversewn, as is the splenic vein stump about 1 cm distal from its confluence with the superior mesenteric vein. Insert: distal pancreas with splenic artery, vein and pancreatic duct (marked with a single fine suture) (from Gruessner 2023, mod.)³.

Upon completion of the donor procedure the viability of the spleen is re-assessed. Only in the rare case of major bleeding from the splenic hilum or large tears should the spleen be removed. The abdomen is closed, and drains should be avoided. The post-operative care of the donor is the same as for any patient undergoing a major abdominal procedure. Donors should routinely be followed

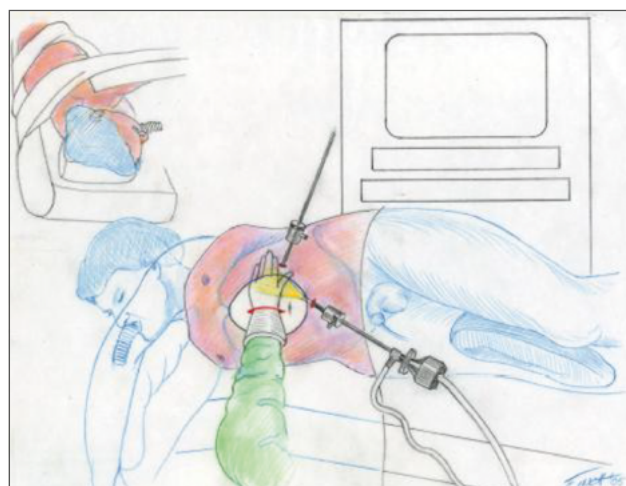


Figure 4. Laparoscopic distal pancreatectomy (living donor): The donor is placed in the right lateral decubitus position (for removal of the left kidney) by using the hand-assisted technique. The surgeon's hand is inside of the abdomen via a supra-umbilical midline incision of 7 cm. Only 2 ports are placed: one para-rectally 2 cm below and slightly left of the donor umbilicus (for laparoscope and camera), the other (instrument port) in the mid-left abdomen (anterior axillary line) (from Gruessner 2023, mod.)³.

in outpatient clinic at 1 and 3 months and every year for plasma glucose, HbA1c and C-peptide check-ups^{5,12}.

Outcome

In contrast to living kidney or living liver donors, the mortality rate of living pancreas donors, according to the International Pancreas Transplant Registry (IPTR), has been 0%¹⁹. The median duration of donor hospitalization in the United States after open distal pancreatectomy is 8 days (range, 6 to 24 days); after laparoscopic distal pancreatectomy, 4 to 6 days¹²⁻¹⁵.

Surgical complications are rare; relaparotomies are required in < 5% of donors. Serum amylase levels postdonation usually return to normal range within 3 days^{5,12}. Most surgical complications are related to the spleen. The incidence of donor splenectomy (intra- and post-operatively) ranges from 10 to 20%^{5,12}. For prophylaxis against overwhelming post-splenectomy infection (OPSI), all donors should receive vaccinations (polyvalent pneumococcus, streptococcus, meningococcus, and hemophilus B) two weeks pre-operatively^{5,12,20}.

The effects of distal donor pancreatectomy on insulin secretion, glucose tolerance, and pancreatic β and α cell function have been extensively studied at the University of Minnesota. Metabolic studies have shown that about 25% of donors after one year displayed abnormal glucose tolerance on an oral glucose tolerance test with reductions in stimulated insulin and glucagon secretion and functional beta cell reserve²¹⁻²⁴.

A 2016 study of 46 donors showed that post-donation 15% had developed diabetes requiring oral hypoglycemics with a mean time of onset of 9.2 ($\pm$ 3.3) years and 11% had developed insulin-dependent diabetes with a mean time of onset of 7 ($\pm$ 5.4) years²⁵. Interestingly, the recipient graft failure rate in this study was significantly higher for the recipients whose donors went on to become diabetic: 75 vs 39% for non-DM donors^{5,25}. Based on these results, a risk stratification model was proposed to predict the risk for the development of post-donation diabetes mellitus (Tab. III). This risk stratification model showed that the presence of 2 or greater RFs was associated with 100% rate of becoming diabetic postdonation; at the same time, none of the donors with "0" RFs became diabetic²⁵. These comprehensive follow-up studies are an important tool in the work-up and counselling of potential donors and further reduction in the incidence of post-donation diabetes mellitus.

Quality of life studies

Two post-donation quality of life surveys demonstrated that pancreas donors stood by their decision to donate. On the question "would you do it again", more than 85% of donors responded "definitively"^{5,23,25}.

THE RECIPIENT

Work-up

The pretransplant evaluation of the candidate for a living

donor pancreas is no different than for a deceased donor pancreas. It comprises medical, psychological, and social evaluations²⁶. The recipient must be well informed about the risks and benefits of the procedure and understand the basic aspects of the evaluation.

As part of the medical evaluation, cardiac and vascular risk assessments are pivotal²⁷. Because diabetes is a major risk factor for coronary artery disease (CAD), coronary angiograms or CTAs should be performed in most, but specifically in uremic, candidates. If on vascular examination vascular insufficiency of the lower extremity is found, it may need to be corrected pretransplant since the transplant may further diminish lower extremity arterial flow. Vascular disease of the iliac arteries, if suspected, should be looked for using a Doppler ultrasound. A follow-up magnetic resonance angiogram (MRA) or a contrast angiogram may be indicated^{26,27}.

Notably, 93% of donors were genetically related to the recipient and only 7% were unrelated according to the IPTR.¹⁹ In contrast to kidney or liver transplantation, no altruistic living donors have been used in the Western hemisphere. It is also remarkable that 36% of related donors were HLA identical¹⁹.

Living donor pancreas transplantation: surgical aspects

In contrast to whole-organ transplants from deceased donors, only about 50% of the pancreas is procured from living donors to achieve insulin independence.

Table III. Risk Stratification Model (RSM) for prediction of post-donation diabetes (from Kirchner et al., 2013, mod.)¹³.

Risk factors	Diabetics	Nondiabetics	
FPG $\geq$ 100 mg/dL (n = 4)	100%a	0a	
FPG <100 mg/dL (n = 36)	22%	78%	
Basal insulin $\geq$ 9 μ U/mL (n = 5)	80%a	20%a	
Basal insulin <9 μ U/mL (n = 19)	16%	84%	
OGTT 2 h $\geq$ 120 mg/dL (n = 5)	100%a	0a	
OGTT 2 h <120 mg/dL (n = 30)	17%	83%	
Δ BMI >15% (n = 7)	86%a	14%a	
Δ BMI $\leq$ 15% (n = 32)	19%	81%	
Risk factors	RR	95% CI	P
FPG $\geq$ 100 mg/dL	5.6	(2.4-8.3)	< 0.001
Basal insulin $\geq$ 9 μ U/mL	5.1	(1.6-15.6)	0.005
OGTT 2 h $\geq$ 120 mg/dL	6	(2.6-13.4)	< 0.001
Δ BMI > 15%	4.6	(2.1-10.0)	< 0.001
No. risk factors	Diabetics	Nondiabetics	
0 (n = 21)	0	100%	
1 (n = 8)	75%	25%	
$\geq$ 2 (n = 6)	100	0	

a: $p \leq 0.05$ comparing within the diabetic and nondiabetic groups.

RR: relative risk; 95% CI, 95% confidence interval.

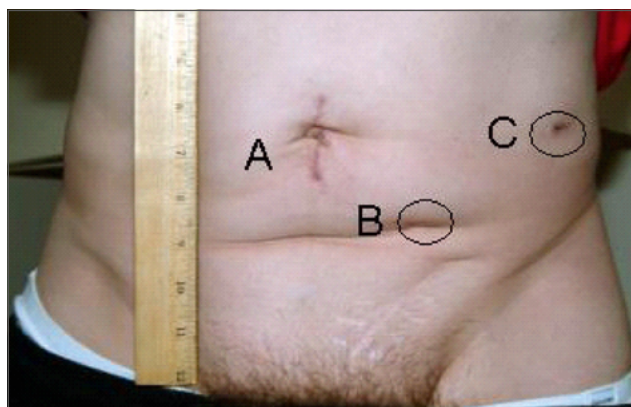


Figure 5. Port sites and midline incision 3 weeks after laparoscopic distal pancreatectomy and left nephrectomy (from Gruessner 2023, mod.)³.

A: midline incision for Gelport® placement;
B: 12-mm camera port;
C: 12-mm working/operative port.

The technical aspects of living donor pancreas transplants are both similar and different than for deceased donor transplants⁴. Like deceased donor transplants, living donor grafts are also implanted intraabdominally and preferably on the right side. Pancreatic exocrine secretions are either enteric or bladder drained and systemic venous drainage is preferred over portal venous drainage (Figs. 6-7). The most physiologic technique for draining pancreatic exocrine secretions is enteric drainage, which – in contrast to bladder drainage – is associated with no technique-related metabolic or urologic complications. The reason why bladder drainage is still being used specifically in solitary (PTA, PAK) living donor transplantation is twofold: (1) ability to monitor urinary amylase levels as a marker for rejection and (2) containment of surgical complications to the lower abdominal quadrant in case of an anastomotic leak⁴. Other techniques for management of exocrine pancreatic secretions, such as ureteral drainage, duct injection, or duct ligation, have rarely been used^{4,19,28}.

The living donor segmental transplant can be placed in a caudad or cephalad position. Creation of a Roux-en-Y loop for enteric drainage is recommended. Unlike deceased donor transplants, living donor grafts are anastomosed to the external (rather than common) iliac vessels with the recipient iliac artery in a lateral (rather than medial) position to best align with the donor splenic vessels. Portal vein drainage has rarely been used for living donor pancreas transplants due to its greater technical complexity⁴.

Because of the shortness and small diameter of the donor vessels, the vascular anastomoses demand meticulous technical skills as do the pancreatico/ducto-enterostomy or pancreatico/ducto-cystostomy. Hence, the two most dreaded complications are vascular thrombosis and

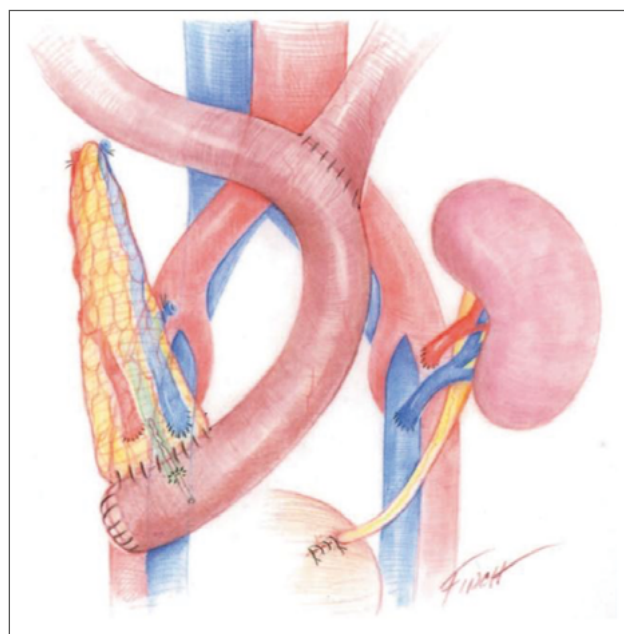


Figure 6. Living donor segmental pancreas transplant with systemic vein and bowel exocrine drainage via a Roux-en-Y loop: The donor's splenic artery and vein are anastomosed end-to-side to the recipient's external iliac artery and vein. The splenic artery anastomosis is lateral and proximal to the splenic vein anastomosis. A 2-layer ducto-jejunostomy or pancreaticojejunostomy (telescope or invagination technique) is constructed side-to-side; about 40 cm distal to that anastomosis, a jejunojunctionostomy is created in standard fashion.

The ureter of the simultaneously transplanted kidney is implanted into the bladder, using the extravesical ureteroneocystostomy (Lich) technique (from Gruessner 2023, mod.)⁴.

pancreatic leakage^{5,12,20,29}. Aggressive systemic anticoagulation during and after the transplant procedure are key to lasting success. To diminish the risk of graft thrombosis, recipients receive 20 to 50 U/kg of heparin during the transplant procedure, prior to vascular clamping. While still in the operating room, before closure of the abdominal incision, recipients are then started on a heparin drip (usually 200 U/hour). The target PTT within the first 24 hours is 40 to 70. In addition, recipients are started on Aspirin 81 mg once a day (for life) and Coumadin on posttransplant day 3 (and continue for up to 6 months with a target INR of 2 to 2.5). The heparin drip is usually discontinued on post-transplant day 5^{5,7,12}.

Post-transplant graft function is usually assessed by closely monitoring plasma glucose levels; insulin must be administered if plasma glucose levels exceed 120 mg/dL. Immunosuppression is initiated in the operating room; the first dose of antibody therapy is usually given before graft reperfusion. Standard immunosuppressive protocols consist of quadruple immunosuppression for induction

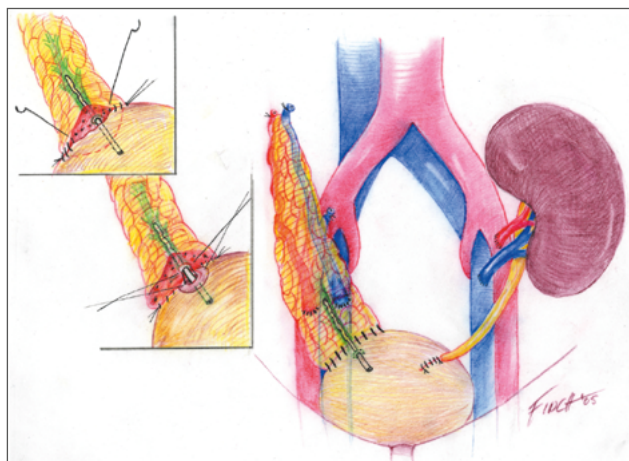


Figure 7. Living donor segmental pancreas transplant with systemic vein and **bladder exocrine drainage**: the donor's splenic artery and vein are anastomosed end-to-side to the recipient's external iliac artery and vein. The splenic artery anastomosis is lateral and proximal to the splenic vein anastomosis. A 2-layer ductocystostomy (inset B) is constructed. The pancreatic duct is sutured to the urothelial layer (inner layer) using interrupted 7-0 sutures over a stent. Alternatively, a 2-layer pancreaticocystostomy can be constructed (inset A): the cut surface of the pancreas is invaginated into the bladder (telescope anastomosis). The ureter of the simultaneously trans-planted kidney is implanted into the bladder, using the extravesical ureteroneocystostomy (Lich) technique (from Gruessner 2023, mod.)⁴.

and triple immunosuppression for maintenance therapy. For induction, anti-T-cell agents are given in combination with a calcineurin inhibitor (tacrolimus), an antimetabolite (mycophenolate mofetil), and steroids.

Antimicrobial prophylaxis, usually initiated perioperatively, consists of antibacterial, antifungal, and antiviral medications. Most recipients, in the absence of complications, are discharged from the hospital within 7 to 11 days post-transplant^{5,7,12}.

Outcome

Patient survival for living donor pancreas recipients in the United States has been high since the beginning, irrespective of the immunosuppressive era. In the tacrolimus era, 1- and 5-year patient survival rates for SPK recipients with living donors according to the IPTR were 100% and 97%; for SPK recipients with deceased donors, 96% and 87% (Fig. 8)^{5,19}. Graft survival rates in the United States at 1- and 5- years in the tacrolimus era for SPK recipients with living donor organs according to the IPTR were 86% and 72%, respectively, vs 85 and 73% with deceased donor organs (Fig. 9)^{5,19}.

Of note are the excellent long-term results of living donor pancreas transplants despite the high vascular thrombosis rates in the AZA and CSA eras. In total, 8 recipients

have enjoyed graft function and insulin independence for ≥ 20 years; 22, for ≥ 15 years; and 44, for ≥ 10 years. Equally remarkable is the fact that of donors whose recipients have had a functioning graft for ≥ 10 years, 11 (25%) were HLA-identical siblings and 2 (2%) were identical twins. Thus, for successful long-term PTA and PAK graft function, HLA matching still has an impact.

Quality of life

In a small quality of life study involving 14 SPK recipients at the University of Minnesota, all 14 felt their general health posttransplant (vs pretransplant) was improved. When asked if they would elect another transplant if they lost graft function, 13 of the 14 recipients said yes¹².

THE IDENTICAL TWIN TRANSPLANT EXPERIENCE

The autoimmune nature of diabetes mellitus is based on several independent observations, including (1) the presence of a lymphocytic infiltrate in the islets ("isletitis"), (2) the appearance of a series of autoantibodies coupled with a progressive loss of insulin secretion, (3) the specificity of pancreatic β -cell destruction, and (4) recurrence of type 1 diabetes mellitus in patients transplanted with identical twin pancreas grafts in the absence of immunosuppressive therapy^{30,31}.

In the University of Minnesota experience, 10 pancreas transplants were performed between monozygous twins. Of those, 3 thrombosed and 7 were technically successful. The first three recipients were not given any induction or maintenance immunosuppression. Once progressive hyperglycemia was diagnosed within 5 to 12 weeks

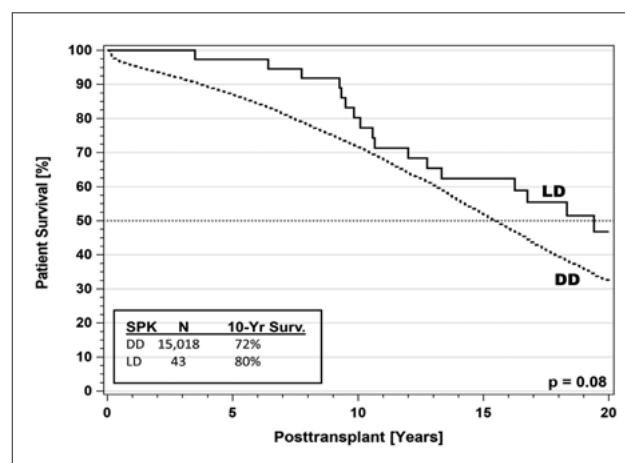


Figure 8. Patient survival for primary SPK transplants (living vs deceased donors) in the tacrolimus era (from Gruessner 2023, mod.)⁶.

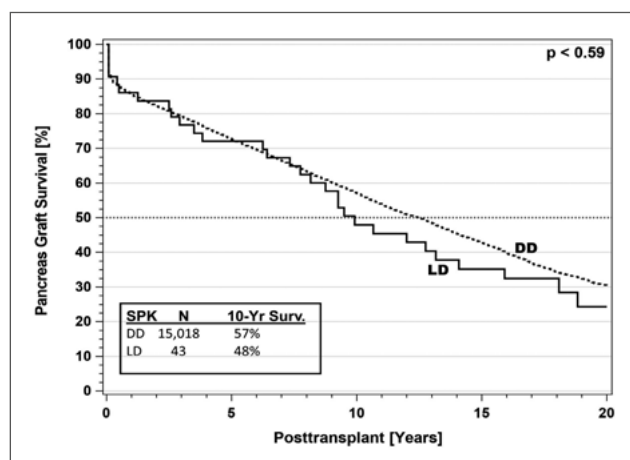


Figure 9. Pancreas graft survival for primary SPK transplants (living vs deceased donors) in the tacrolimus era (from Gruessner 2023, mod.)⁵.

post-transplant, anti-rejection treatment did not change the course to graft failure. Pancreas graft biopsies obtained after loss of graft function revealed selective destruction of all β cells (Fig. 10)^{5,30,31}. Hence, selected β -cell destruction was a consequence of β -cell-mediated immunity leading to recurrent diabetes mellitus.

The fourth identical twin pancreas recipient was prophylactically given AZA post-transplant. A biopsy at 6 weeks posttransplant, however, showed mild isletitis without β -cell destruction. At 36 months posttransplant, another biopsy showed resolution of isletitis, but destruction of β cells in 70%. CSA was added to the immunosuppressive regimen. At 5 years post-transplant, the recipient became fully insulin dependent^{5,30,31}.

Of the last three solitary identical twin pancreas transplants, done between 1987 and 1990, 2 recipients were given induction therapy with Minnesota ALG, and all three were maintained on CSA-based maintenance therapy. Of those, one lost the graft due to rejection at 4 years, one showed partial function at 15 years, and one has remained normoglycemic for over 16 years.

This unique surgical experience, in itself, lent strong evidence to diabetes mellitus being an autoimmune disease even before the time when advanced laboratory techniques became available²⁹⁻³². It also demonstrated that the disease recurrence in the absence of immunosuppressive therapy can occur as early as several weeks posttransplant and that low-dose immunosuppressive therapy cannot prevent disease recurrence. Furthermore, immunosuppression given late (i.e., months or years after the clinical onset of diabetes mellitus) does not allow β -cell regeneration. The fact that immunosuppression prevents recurrence of disease in pancreas transplant recipients means that it should also prevent progression of disease in de-novo

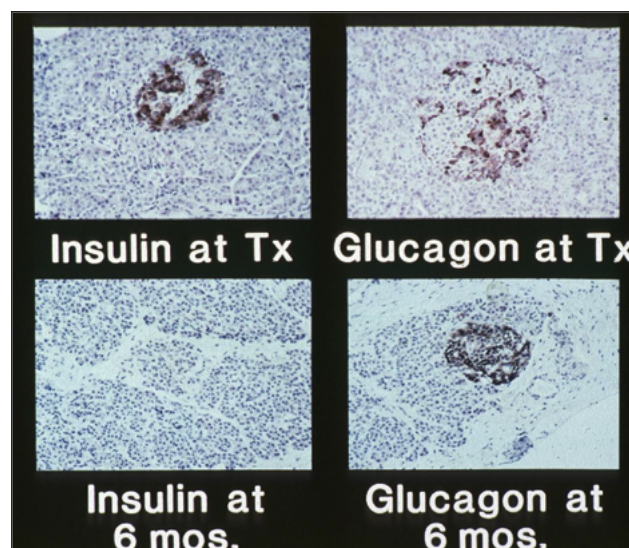


Figure 10. Identical twin transplants: Selective β -cell loss and normal α -cells in a patient without immunosuppression 6 months after the transplant (from Gruessner 2023, mod.)⁵.

autoimmune diabetes mellitus if applied early enough. Such a study, preferably done in children who carry a genetically high risk to develop diabetes mellitus, has not been done because of the concern of immunosuppressive side effects.

SUMMARY

Even though living donor pancreas transplants remain rare procedures, they are part of the armamentarium that offers diabetic patients a life without exogenous insulin administration. At the First World Consensus Conference on Pancreas Transplantation, held in Pisa, Italy, from October 17-19, 2019, it was concluded that “live donor segmental pancreas transplantation is an option in immunized patients in extremely well selected pairs provided that the center is able to ensure quality of the procedure and careful lifelong follow-up of the donor”³³.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Both authors contributed equally to the manuscript.

Ethical consideration

Not applicable

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