Innovations in pancreas transplantation

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ABSTRACT

Pancreas transplantation is currently the curative treatment for type 1 diabetes mellitus. It aims at providing physiological insulin replacement therapy in type 1 diabetes mellitus. The goal is thereby also to prevent secondary complications of diabetes. Long term control of glucose metabolism has only been achieved by pancreas transplantation. As a result of improvements in the surgical techniques and the efficacy of immunosuppression, the patient and graft survival rates have improved dramatically over the last 2 decades. As a result, pancreas transplantation, as part of simultaneous pancreas and kidney transplantation, pancreas after kidney transplantation, and exceptionally pancreas transplantation alone, became the standard therapeutic option for patients with type 1 diabetes mellitus with end-stage renal disease. In this article we review the pancreas transplantation methods, indications, techniques, and the short as well as the long outcomes of treatment.

Keywords: Pancreas transplantation, simultaneous pancreas and kidney transplantation, pancreas after kidney transplantation, pancreas transplantation alone.

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Pancreas transplantation (PTx) is unique among the vascularized organ transplants: Instead of being used to save life, it attempts to stabilize or prevent the devastating target organ complications of type 1 diabetes mellitus (T1DM). The first clinical PTx in a human was performed by Kelly and Lillehei on December 17, 1966.[1] It was a segmental graft transplanted to the iliac fossa, with the pancreatic duct ligated. In 1973, Gliedman et al[2] first suggested the use of the urinary tract for exocrine drainage. In the mid-1970s Groth et al, at the Huddinge Hospital in Stockholm, embarked on a large series of enterically drained grafts.[3] A new method of handling exocrine secretions was suggested by Dubernard et al,[4] at Herriot Hospital in Lyon, who suggested that exocrine secretion could be obliterated by injecting the pancreatic duct with a polymer. In 1982, Cook and Sollinger, from the University of Wisconsin, suggested channeling the exocrine secretions to the urinary bladder. In their initial clinical experience, the pancreatic duct of the segmental graft was sutured to the bladder mucosa. They then turned to whole pancreas grafts, using the duodenal button technique and to the doudenal segment method as described by Nghiem et al.[5] A return to the original method of Lillehei et al,[6] in which a whole pancreas transplant was used with anastomosis of graft duodenum to the recipient bowel, was reintroduced in the 1980s.[7] Since then, PTx developed rapidly and became a standard treatment for T1DM patients especially those with end-stage renal disease (ESRD) for whom kidney transplantation is also performed simultaneously or before the PTx.

Insulin controls blood glucose within a very narrow range that cannot be constantly achieved by conventional insulin usage, parentral insulin, open-loop-systems, for example, portable pumps, or artificial endocrine pancreas. There is always the risk of hypoglycemia or ketoacidosis. Intermittent hyperglycemia is responsible for the development of

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microvasculopathy that leads to lesions which, affect retina, kidneys, nerves, and other systems.[8] By 20 years after onset of diabetes, more than 50% of individuals with T1DM are either blind, in renal failure, or have sensory or motor disturbances.[9,10] The annual incidence of T1DM in the United States of America (USA) and Europe is approximately 55 new cases per million population, the majority develops in children.[10,11] These patients usually live longer, so they have a higher chance of suffering from the chronic complications in life, of which ESRD is a major one. For these patients, combined pancreas/ kidney transplantation, whether simultaneous or consequential, has become a standard treatment. Pancreas transplantation alone in non-uremic T1DM patients is exceptionally carried out in few centers. Despite recent advances, islet transplantation is far from being a routine clinical practice with predictable results. More than 300,000 cells are needed to be transplanted, and islet purification leads to the destruction of islet cell precursors,[12] so several donors are required to obtain a sufficient number of islets for successful transplantation into a single recipient.[13] In addition, there are potential complications associated with the procedure of injection of these cells in the body, including portal vein thrombosis. Patients, after islet cell transplantation, still need immunosuppression and it is more difficult to monitor these patients for rejection. The 1990-1995 data from the International Islet Transplant Registry[14] indicates that only 6% of type 1 diabetic recipients of islet cells achieve exogenous insulin independence more than one year.

Indications. Although patients with T1DM are the candidates for PTx, the indications for transplanting the pancreas remain controversial. It can be performed in 3 settings: alone in a patient with near normal renal function (Pancreas transplantation alone - PTA), after successful kidney grafting (Pancreas after kidney transplantation - PAK), and simultaneously with a kidney transplant (Simultaneous pancreas and kidney transplantation - SPK). In PTA, the aim of transplantation is to prevent the development of diabetic secondary complications, such as nephropathy, retinopathy, or neuropathy. In the absence of indications for kidney transplantation, PTx should considered a therapy in patients who exhibit these 3 criteria: 1. a history of frequent, acute, and severe metabolic complications (hypoglycemia, hyperglycemia, ketoacidosis) requiring medical attention, 2. clinical and emotional problems with exogenous insulin therapy that are so severe as to be incapacitating 3. consistent failure of insulin-based management to prevent acute complications.[15] In general, PTx in a preuremic patient is justified in a setting where careful long-term monitoring of its potential effect on secondary complications can be performed. In PAK, the recipients have usually undergone successful living-donor kidney transplantation, then, they have PTx with cadaveric pancreas graft. They are performed in order to prevent the recurrence of nephropathy in the graft, as well as the other benefits of PTx. The advantages of transplanting the pancreas after successful transplantation of the kidney is that the patient is already on immunosuppressive therapy. Unfortunately, the results of sequential grafting are inferior to that of SPK. For this reason most PTx have been combined transplants, such as SPK. Today, SPK is the most common procedure of PTx in practice. In this setting, one surgical procedure is required, and the patient receives an immunosuppressive regimen similar to that of a patient undergoing a kidney transplant alone. There is little information on what should be carried out for patients who have ESRD, but whose diabetes millitus (DM) is type 2 as defined by C-peptide status. It has been reported that SPK transplants in patients with ESRD secondary to DM, have equivalent outcomes regardless of diabetes type.[16, 17]

Selection of the recipients. Type 1, C-peptide deficient, insulin-dependent diabetics younger than 55 years of age are considered potential recipients for PTx.[18] The T1DM must be present for the last 5 years. For SPK, the patients are uremic with creatinin clearance of less than 20 ml per minute. The usual range of age of recipients is 15-55 years, although PTx has been reported at 5 months and 65 years of ages.[19] Other inclusion criteria are evidence of progressive diabetic complications such as retinopathy, neuropathy, and so forth, brittle diabetes with significant impairment of lifestyle with glycosylated hemoglobin (HbA1c) results higher than 8%, motivated and compliant patients, informed consent, and absence of any absolute contraindications (**Table 1**). The absolute

Table 1 - Absolute and relative contraindications for different types of pancreas transplantation.

Absolute contraindications	Relative contraindications
Presence of malignancy (active)	History of noncompliance
Insufficient cardiac reserve	History of cancer with no active disease in this time
HIV positive	History of an infection
Ongoing substance abuse	Pregnancy
Major ongoing psychiatric illness	History of psychiatric illness
Active systemic infection	Significant obesity
Major chronic pulmonary disease	History of substance abuse

HIV - human immunodeficiency virus

Table 2 - Pre-transplantation work-up for the recipients of pancreas transplantation.

General evaluation

Complete history, specially past history.
Physical examination.
Usual blood tests: FBC with differential, U&E, LFT, coagulation profile, calcium, magnesium, blood grouping, lipid profile, and immunological screening; ANA, ASA.
Nephrological screening; urine culture, U/S of the native kidneys, residual urine volume.
Bone screening; PTH, bone x-ray of one hand, corneal calcification.
Hepatitis screening; HAV, HBV, HCV, HDV.
Viral screening; CMV, EBV, HSV, HIV.
Stomatology examination; dentistry consultation.

Evaluation of the diabetes

Immunology
- HLA typing (HLA-B7, -B8, -B13, DR-3, DR-4)
- Screening for islet cell antibodies, thyroid cell antibodies, insulin antibodies, parietal cell antibodies

Residual secretion
- Oral glucose tolerance test
- Metabolic profile with C-peptide level
- Glucagon test (1mg IV) with C-peptide level (only if questionable diagnosis between type 1 and type 2 DM).

Stability of the diabetes
- Glycosylated hemoglobin

Other levels
- Amylase, lipase
- Thyroid hormones
- Diabetologist consultation

Evaluation of diabetic complications

Cardiac
- ECG
- CXR
- Echocardiogram
- Coronary angiography (optional)
- Dobutamine stress Echocardiogram
- Cardiac consultation

Ophthalmology
- Visual acuity
- Slit lamp examination
- Fundoscopy
- Fluorescein angiography
- Ophthalmology consultation

Genitourinary
- Voiding cystogram
- Renal biopsy (optional)

Neurology
- EMG
- Nerve conduction velocity
- Autonomic nerve function assays (by 24 hour holter monitoring the heart rate variability).
- Carotid Doppler

Final evaluation:
- Surgeon
- Diabetologist
- Nephrologist
- Anesthesiologist

FBC - full blood count, U&E - urea and electrolytes, LFT - liver function test, ANA - antinuclear antibodies, ASA - acetylsalicylic acid, U/S - ultrasound, PTH - parathyroid hormone, HAV - hepatitis A virus, HBV - hepatitis B virus, HCV - hepatitis C virus, HDV - hepatitis D virus, CMV - cytomegalovirus, EBV - Epstein-Barr virus, HSV - herpes simplex virus, HIV - human immunodeficiency virus, HLA - human leucocyte antigen, DM - diabetes mellitus, ECG - electrocardiogram, CXR - chest x-ray, EMG - electromyogram, IV - intravenous

contraindications for PTx are similar to those of kidney transplantation and include the presence of malignancy and active infection. Patients with advanced cardiovascular disease, major amputation, and inability to understand the nature of the procedure are also excluded from PTx. For absolute and relative exclusion criteria of the recipient see **Table 1**. The patient, who is referred for SPK, should initially fulfil the requirements before he is scheduled for pre-transplant work-up. After the patients are accepted for PTx, they go through the pre-transplantation work-up, which is similar to the pre-transplantation evaluation for kidney transplantation alone **(Table 2).** Identical blood group and negative cross matching are essential to match the graft to a specific recipient. Human leucocyte antigen (HLA) typing was found to have no effects on the outcomes of SPK, but it affects the graft survival in PAK and PTA.[20]

Donor selection. The pancreas graft donor is usually cadaveric whether heart-beating or non heart-beating cadavers. In a few centers, they used living-related donors for the pancreas graft, that is a segmental pancreas graft including the pancreas tail and part of the body, and kidney (living-related simultaneous pancreas-kidney transplantation-LRSPK).[21] The criteria for donor selection of pancreas graft are similar to that of kidney graft, for cadaveric donors. Any donor who is suitable for multi-organ donation is a potential candidate for pancreas donation. Exclusion criteria for renal graft donors are also exclusion criteria for pancreas as both organs are taken for one recipient. The exclusion criteria for pancreas donation includes: age > 55 years or < 10 years, history of DM, history of chronic alcohol consumption, malignancy (except skin or central nervous system), chronic infections (such as hepatitis, tuberculosis, syphilis, HIV), or intravenous drug abuse, prolonged episodes of hypotension or high dose vasopressor use, and acute systemic infection. The intra-operative exclusion criteria includes tumor, trauma, pancreatitis and abnormalities of the pancreas on gross inspection. Acutely elevated plasma glucose and serum amylase are not exclusion criteria for pancreas transplant donors. Direct inspection of the pancreas is necessary to establish whether or not the pancreas may be used for transplantation.

Donor management. Pre-operative care of the pancreas donor is, in general, similar to that of a liver/kidney donor. Vasopressive agents should be avoided and fluid replacement regulated with the aid of a central venous pressure (CVP) monitor, urine out put, and electrolyte balance. Subcutaneous insulin is given, when required, q 4 hours based on the blood sugar. Bowel decontamination is attempted in all cases where possible, at the time that the responsibility for donor care is assumed by the

Table 3 - The checklist of the donor before the starting of the procurement procedure.

The checklist before the procurement procedure including
The consent for donation.
The confirmation of brain death by 2 consultant intensivist doctors
The cause of brain death.
Time of ICU stay.
Drug list that the donor is receiving currently, especially the vasopressors.
Demographic data of the patient, for example, age, sex, weight, height, History of the patient
Last vital signs including CVP, Fluid balance, and nursing data.
Investigations:
Radiological:
CXR
Abdominal U/S
Any others were done.
Laboratory:
FBC
Coagulation profile
Serum electrolytes
Renal functions, creatinin, BUN
Liver functions
Serum Amylase, and Lipase
Viral screening:
HIV
HbsAg
HbsAb
HbcAb
HCAb
HDV
CMV IgG
Check the intended organs to be harvested
Examine the patient on the operating table.
Check your instrument, perfusion sets, availability of the required drugs, and assisting surgeons.

ICU - intensive care unit, CVP - central venous pressure, CXR - chest x-ray, U/S - ultrasound, FBC - full blood count, BUN - blood urea nitrogen, HIV - human immunodeficiency virus, HbsAg - hepatitis B surface antigen, HbsAb - hepatitis B virus surface antibodies, HbcAb -hepatitis B virus core antibodies, HCAb - hepatitis C virus antibodies, HDV - hepatitis D virus, CMV - cytomegalovirus, IgG - immunoglobulin G

transplant coordinator. Systemic antibiotics, other than those the donor is already receiving, are given just prior to the donor being taken to the operating room. In addition, the donor should receive methylprednisolone, pre-procurement, and heparin, just before the prefusion. Before the start of the procurement procedure the checklist of the donor should be examined (**Table 3**). The points in the checklist must be fulfilled before the donor is brought to the operating room. The procurement procedure on the donor starts with a median sterno-laparotomy, followed by explorative laparotomy of the abdominal contents. The lesser sac is approached through the division of the gastrocolic ligament, opening the lesser sac, then the pancreas is closely examined. The non-touch technique during the pancreas procurement is essential to avoid any manipulation trauma to the organ. The pancreas is harvested together with the spleen attached to it, and the spleen is used to handle the pancreas graft. The donors of the pancreas are usually good donors for the liver, so that the pancreas can be harvested with or without the liver graft. When the pancreas and liver are going to be harvested, the pancreas is either taken combined with the liver and then both organs are separated on the backtable, or they are separated in-situ and procured as isolated organs. Most pancreatic grafts are procured as whole organ grafts, occasionally segmental pancreatic graft can also be used, especially in living-related pancreas transplantation as part of SPK, PAK, or PTA.[21] The whole pancreas organ is usually harvested in combination with the C-shaped duodenum. The splenic artery is divided at its origin from the celiac trunk and marked with a stitch. The superior mesentric artery (SMA) is taken with a patch from the aorta. The portal vein is divided about one cm above the head of the pancreas in order to keep good length for both grafts, liver and pancreas. After removal of the pancreas from the donor, the arteries of the graft are flushed at a low pressure-below 20mmHg[22] with a volume of preservative solution, such as University of Wisconsin solution, just sufficient for the venous effluent (50-100ml). The pancreas is immersed in the same solution (approximately 400ml) and stored at 4ºC until the time of PTx. The right kidney should then be harvested, in case of SPK, in addition to the vascular grafts which include the Y-shaped part of iliac vessels, artery and vein of one side. The vascular graft must be packed with the pancreas graft, while the right kidney is packed separately and sent with the pancreas graft to the recipient center.

Benching of the graft. When the graft arrives at the recipient hospital, benching of the graft, in a sterile setting in the operating room starts. The pancreatic graft is unpacked and generally examined, for the parenchyma and the vessels. The attached spleen provides orientation for the surgeon. The spleen can be either separated during the benching or after the implantation of the pancreas. The extra-pancreatic fat and tissue are removed. The distal part of the duodenum is shortened as much as possible. The portal vein stump is prepared and freed for venous anastomosis. The Y-shaped iliac artery is prepared for the following anastomosis: the internal iliac artery to the splenic artery, and the external iliac artery to the SMA stump. The renal graft should be benched and prepared for transplantation, especially if the harvesting team is different from the implanting team.

Implantation of the graft. The pancreas graft is usually placed intra-peritoneally at the right iliac fossa. The abdominal incision for pancreas implantation depends on the way, the site, and the setting of the PTx. In SPK, the incision can be either midline laparotomy or right followed by left

Rutherford-Morrison incisions for pancreas and kidney implantations. The implantation starts with the PTx by preparation of the right iliac vessels for the anastomosis. The anastomosis is started with the portal vein to the external iliac vein or inferior vena cava, followed by the arterial anastomosis between the lower limb of the Y-shape iliac artery graft and the common or external iliac artery. These anastomoses are made by the end-to-side technique. The anastomosis site on the iliac vessels usually depends on the pelvis size, the graft size, the graft positioning, and the surgeon preference and experience. The portal vein drainage can be systemic, which is most commonly practiced, or portal. After one year of portal venous drainage or systemic venous drainage, no significant differences with regard to fasting glucose, fasting insulin, oral glucose tolerance test (GTT), glycosylated hemoglobine (HbA1c), cholesterol, or triglyceride could be detected.[23] Systemic drainage rather than portal delivery of insulin results in a baseline fasting hyperinsulinemia. Exocrine drainage of pancreas graft is usually by any of these 3 techniques 1. Enteric drainage 2. Bladder drainage 3. Injection of the pancreatic duct with a polymer 4. other rare techniques. Each of these techniques has its advantages and disadvantages. Currently, the most commonly practiced techniques are bladder and enteric drainages. In general, enteric drainage is the preferred technique in SPK, while bladder drainage is preferred in PAK and PTA for graft monitoring purposes.

Immunosuppression. Avoiding early acute rejection is considered a favorable prognostic sign for good long-term graft function. Pancreas transplantation especially SPK, has become the procedure with excellent results due to 2 major reasons; improvement in surgical technique and introduction of new immunosuppressive agents.[24,25] Several regimens have been tried in different centers.

Table 4 - Immunosuppressive protocol in pancreas transplantation.

Pre-operative	Azathioprine or Mycophenolate mofetil ± Tacrolimus or Cyclosporine A
Induction	Anti-lymphocytes; Polyclonal, ALG or Monoclonal, OKT3 or Anti-IL-2 receptor; Basiliximab or Daclizumab + Steroid
Maintenance	Steroid +Tacrolimus or Cyclosporine A +Mycophenolate mofetil or Azathioprine + 5-7 days Anti-lymphocyte, or 2nd dose of Basiliximab (or 4 doses of daclizumab)

ALG - anti-lymphocyte globulines, OKT3 - ortho-klonal antibodies against T-cell of CD3 type, Anti-IL-2 - anti-interleukine 2.

Most North American transplant centers have adopted the use of Quadruple immunosuppressive therapy **(Table 4).** Cyclosporine A is not nearly as successful in preventing rejection of pancreas allografts as it is with other organs. The best results were with tacrolimus/mycophenolate mofetil (Tac/MMF) plus induction with anti-T-cell in SPK recipients.[26] Most of the programs were started with azathioprine as a 3rd agent and it was replaced by MMF.[27] Recently, trials of steroid withdrawal showed some successful results in order to avoid secondary complications of long-term use of steroids.[27-29] More than 95% of all rejection episodes can be successfully reversed with high-dose steroids, anti-lymphocyte globulines (ALG), ortho-klonal antibodies against T-cell of CD3 type (OKT3), or Tacrolimus retreatment.

Post-operative graft monitoring. Monitoring and management of graft dysfunction are critical to maintaining long-term function. Renal function follow-up is the best monitor for pancreas graft in SPK. Serum amylase, lipase and blood sugar are also used to monitor pancreas graft in all settings, especially in cases of enteric drainage of exocrine secretion. When the serum amylase/lipase and blood sugar increase, these are signs of graft dysfunction. In SPK, renal biopsy is usually sufficient to control the pancreas graft for rejection since almost all rejections of the pancreas occur with renal rejection which can be diagnosed by the renal biopsy. In other settings of PTx, PAK or PTA, especially when the exocrine drainage is in the urinary bladder, urine amylase and blood sugar are used to monitor the pancreas graft. Increase of blood sugar and decrease in urine amylase are signs of graft rejection. Pancreas biopsy is not usually performed, and when it is performed, it is usually in open techniques rather than percutaneous. The biopsy of the pancreas also needs special experience to be examined. Post-operative ultrasound follow up including the examination of the blood flow in the graft is important in order to detect any flow disturbance as early as possible. The ultrasound can also detect any fluid collection or abscess formation in the abdomen or around the graft. Other blood examinations, for example, full blood count, serum electrolytes, and C-reactive protein, are important to monitor the patient in general and the pancreatic graft.

Complications. The most common technical complications in enterically-drained pancreas grafts included a 5% incidence of anastomotic fistula, a 5% incidence of abscess, a 4% incidence of pancreatitis, and a 4% incidence of thrombosis. The incidence of these complications are higher in bladder drained graft.[27] In bladder drained graft there is a higher risk for urinary tract infection, reflux pancreatitis, and metabolic acidosis due to loss of bicarbonates in the urine. The technical complications are less common

as experience in PTx is gained. Acute rejection is a significant cause of graft loss in SPK recipients.[30] It is usually treated with high doses of methylprednisolone or antibodies. Overall causes of deaths in 209 recipients of SPK transplants were cardiac 36%, infections 36%, pulmonary embolism 16%, others 16%.[19] The most common cause of pancreas graft loss were death 38%, thrombosis 31%, rejection 23%, sepsis 8%.[19]

Outcome of pancreas transplantation. As of 2000, more than 14,000 pancreas transplants have been reported to the International Pancreas Transplant Registry (IPTR), including nearly 1500 in 1999.[26] The overall one and 3-year actuarial patient survival rates were 98% and 95%.[27] Similar results were reported from Berlin where the actuarial patient survival at one, 3, and 5 years was estimated at 97%.[31] While the actuarial 10-year survival rates for 136 SPKs were 91.79% (patient), 85.07% (pancreas graft), 83.58% (kidney graft).[17] This represents the good long-term outcome from SPK as it prevents the recurrence of nephropathy in the transplanted graft as well as the secondary complications of T1DM. Ojo et al[32] have performed an observational survival analysis of 13,467 uremic type 1 diabetics who underwent SPK, cadaveric kidney-alone, or living donor kidney transplantation or who remained on the transplant waiting list between October 1988 and June 1997 in the USA. They confirmed that SPK recipients had a life expectancy that was 15 years longer than their waiting-list counterparts and 10 years longer than if they had cadaveric kidney transplantation alone. The survival advantage of SPK was evident across different demographic subgroups except in patients who were 50 years old at the time of transplantation. In other studies, it was confirmed that SPK transplantation prevents the development of diabetic nephropathy in the kidney graft.[33,34] Cadaveric kidney survival rates were higher in SPK recipients than in diabetic recipients of cadaveric kidney alone.[35]

In conclusion, PTx, especially SPK, provides the available curative treatment for well-selected uremic type 1 diabetics. It has very good short and long-term survival rates for both the patient and the grafts. It also improves the quality of life of the recipients. Simultaneous pancreas and kidney transplantation and other types of PTx procedures should be the treatment of choice especially in countries where there is a very high incidence of DM.

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