CHAPTER 30

PANCREATIC TRANSPLANT IN DIABETES

Afshin Tavakoli*,[1] and Sue Liong[2]

Departments of [1]Renal and Pancreas Transplantation and [2]Clinical Radiology, Manchester Royal Infirmary, Manchester, UK

**Corresponding Author: Afshin Tavakoli—Email: afshin.tavakoli@cmft.nhs.uk*

Abstract: Whole organ pancreas transplantation is increasingly being performed for the treatment of diabetes mellitus. To date, over 32,000 pancreas transplants have been performed worldwide. The procedure is associated with significant mortality and morbidity in early transplant period. However, the successful pancreas transplantation has the potential to render patients insulin-independent and halt the progression of complications of diabetes, thereby improving both quality of life and patient survival.

INTRODUCTION

Whole organ pancreas transplantation is increasingly being performed worldwide for the treatment of diabetes mellitus (DM). The first successful pancreas transplantation was performed in conjunction with simultaneous kidney transplantation by Dr Richard Lillehei, from the University of Minnesota in 1966.[1] Until 1990, the procedure was considered experimental, but now it is a widely accepted modality for the treatment of DM.

The pancreas is provided by cadaveric organ donors although selected cases of living-donor pancreas transplantations have been performed in North America. To date, over 32000 pancreas transplants have been performed worldwide, with the majority of these cases performed in the United States of America (USA). Approximately 10000 transplants have been performed outside the USA. Europe stands with 6766 pancreas transplantations, followed by Latin America with 1945, Canada with 671, Oceania with 499, Asia with 222 and Africa with 5. These countries together account for annual activity of about 1100 pancreas transplants in comparison to over 1200 cases which are performed annually in the USA alone.[2]

Diabetes: An Old Disease, a New Insight, edited by Shamim I. Ahmad.

WHOLE ORGAN PANCREATIC TRANSPLANTATION PROCEDURES

There are three main categories of whole pancreas transplantation procedures:

1. Simultaneous pancreas and kidney transplant (SPK)—pancreas and kidney (usually from the same deceased donor) are transplanted at the same operation. This is the most commonly performed procedure.
2. Pancreas-after-kidney transplant (PAK)—donor pancreas is transplanted after a previous successful donor kidney transplant. This is the second most commonly performed mode of pancreatic transplant.
3. Pancreas transplant alone (PTA)—donor pancreas transplanted only, usually performed in Type 1 diabetic patients with frequent severe hypoglycemic episodes (hypoglycaemic unawareness), but with preserved renal function.

THE ROLE OF PANCREATIC TRANSPLANTATION

Whole organ pancreas transplantation is currently the only treatment which can produce complete long-term insulin independence and restores a normoglycaemic state. Studies have shown superior survival rates in patients following pancreas and kidney transplantation compared with patients with kidney transplantation alone.[3-5] In addition to improving patient survival rates, simultaneous kidney and pancreas transplantation has also been shown to benefit survival of the kidney graft.[5]

Pancreas transplantation has been associated with positive effects on the long-term complications of diabetes. Following pancreatic transplantation, reversal of peripheral neuropathy has been reported.[6] Pancreas transplantation also has the potential to stabilise advanced diabetic retinopathy[7] and can reverse the diabetic changes in the native kidneys of patients with early diabetic nephropathy.[8]

RECIPIENT SELECTION AND WORK-UP

The number of pancreas transplants is limited by the number of cadaveric organs available for transplantation. Patients with both Type 1 and 2 diabetes are considered for the pancreas transplant if they have, or are at high risk of developing secondary complications, have disabling or life-threatening hypoglycaemic unawareness, or are likely to develop these and are judged to be fit enough to survive the operation.[9]

Ninety-five percent of pancreas transplantations are performed in diabetic patients with renal disease or a previous functioning kidney transplant. The recipients must be fit enough to undergo the surgical procedure. Therefore, the pretransplantation work-up emphasises detection of significant cardiovascular disease, nontreatable infectious disease, and cancer.

Key elements in the history include:[10]

- Renal disease: Transplantation at predialysis stage is the most beneficial.
- Retinopathy: Diabetic retinopathy is a ubiquitous finding in patients with diabetes and endstage renal disease (ESRD): Also significant vision loss may be observed. Although this rarely adversely affects transplant, it is useful to confirm that the patient with significant vision loss has adequate support systems in place to facilitate travel to hospital and ensure immunosuppressive medication compliance.

- Coronary artery disease (CAD): This is the most important comorbidity to consider. Diabetic patients with ESRD carry higher risk of cardiovascular problems than the general population. They usually also have several risk factors in addition to diabetes for development of CAD, including hypertension, hyperlipidaemia, and smoking.
- Cerebrovascular disease: Patients with ESRD and diabetes also experience an increased rate of cerebrovascular disease.[11] Deaths, related to cerebrovascular disease, are approximately twice as common in patients with diabetes compared to patients without diabetes once ESRD has occurred.
- Peripheral vascular disease: Lower extremity peripheral vascular disease is present significantly in patients with diabetes; for example patients with ESRD are at risk of amputation of the lower extremity.
- Autonomic neuropathy: Autonomic neuropathy is prevalent and may manifest as neurogenic or orthostatic hypotension, neurogenic bladder and gastroparesis.
  - In the posttransplant period, blood pressure control may be challenging in patients with orthostatic hypotension.
  - Diabetic patients with neurogenic bladders are at increased risk of renal allograft dysfunction as high bladder volumes can result in vesico-ureteric reflux. This is more significant in patients with bladder drainage of pancreatic graft secretions (discussed later in this chapter).
  - Gastroparesis: Impaired gastric emptying is an important consideration because of its significant implications in the posttransplant course. Patients with severe gastroparesis may have difficulty tolerating oral immunosuppressive medications that are essential to prevent rejection of the transplanted organs.
- Sensory and motor neuropathies: These may have implications for rehabilitation after transplantation.
- Mental or emotional illnesses: A thorough evaluation of psycho-social issues of the patient and support systems available should be undertaken to determine conditions that may jeopardise the outcome of transplantation, such as noncompliance with immunosuppressants.

Pretransplant recipient laboratory evaluations are outlined below:

- Blood group
- Blood chemistry
- Liver function tests
- Full blood count
- Co-agulation profile
- Human Leucocyte Antigen (HLA) typing

For infection screening, serologies for the following are performed:

- Hepatitis B and C virus
- Human immunodeficiency virus (HIV)
- Cytomegalovirus (CMV)
- Human T-cell Lymphotropic virus (HTLV)
- Epstein-Barr virus (EBV)

Further tests that may be performed include:

- Urinalysis
- Urine culture (when there is suspicion of urinary tract infection)
- 24-hour urine test for protein, microalbuminuria and creatinine clearance
- Estimated Glomerular Filtration Rate (GFR)/Radioisotope GFR
- Chest radiography
- Exercise/dipyridamole thallium scintigraphy (Myoview®)
- Coronary arteriography (if indicated)
- Stress echocardiogram (if indicated)
- Fasting and stimulated C-peptide levels
- 12-lead ECG prior to transplantation as base line
- Cardiopulmonary exercise test (CPET)

PANCREATIC PROCUREMENT AND ALLOCATION

Procurement

The National Organ Retrieval Services (NORS) was established in 2010 in United Kingdom to facilitate organ retrieval. As a part of NORS there are currently 7 abdominal teams responsible for multivisceral abdominal organ retrieval including pancreata identified for donation.

Over 90% of pancreas grafts are from deceased heart beating donors. Almost all cadaveric donors suitable for pancreas retrieval will also be suitable for liver retrieval, but not all liver donors will be suitable for pancreas retrieval. Pancreatic tissue (pancreata) from nonheart beating donors have been successfully transplanted with good outcomes.

Surgical procedures vary between institutions, but the underlying principles are similar. The pancreas is retrieved from the donor and transplanted, ensuring adequate vascular supply and drainage of pancreatic secretions.

The liver, spleen and pancreas are anatomically closely related structures, sharing important vascular supply. The pancreas can be retrieved 'en bloc' with the liver and spleen or without the liver. The 'en bloc' retrieval technique is rarely practised in UK. All donors are considered for pancreas donation and if a pancreas is not suitable for whole organ transplantation, it can then be considered for islet cell transplantation, a procedure which will be discussed later in this chapter.

Unless there are other contra-indications, current UK guidelines suggest that donors should be between 6 and 60 years of age.

In the early years of multi-organ retrieval, certain variations in the arterial anatomy of the liver were regarded as contra-indications to pancreas retrieval. However, this is no longer the case. Familiarity and knowledge of variations in vascular anatomy have allowed successful retrieval of both pancreas and liver from virtually all cadaveric donors. The 'en bloc' retrieval technique may offer advantages in donors with certain anatomic variations.

Pancreas Retrieval Surgery

Access to the pancreas is through opening the lesser sac. This is achieved through dividing the gastrocolic ligament from the pylorus up to the spleen.

Good exposure is essential for adequate and thorough pancreas assessment as well as preventing any damage to the pancreas during retrieval. The suitability of the pancreas depends on the detailed examination of the organ at the time of procurement. The examination should include assessment of:

- Colour of the pancreas (the normal pancreas is salmon pink, a yellow colour suggests fatty infiltration).
- Pancreatic size
- Texture of the pancreas by gentle bimanual palpation. The normal pancreas is soft and elastic. A hard pancreas suggests fibrotic changes. Irregularity or nodularity in the pancreas should raise suspicion of chronic pancreatitis or tumour.
- Signs of inflammation, congestion or any other pathology.
- Degree of steatosis, peripancreatic fat, intra-acinar and intra-paranchymal adipose deposition. It is important to distinguish between intra-parenchymal and subcapsular fat. In the presence of subcapsular fatty infiltration, the pancreas can be used for solid organ transplant. In contrast, intra-parenchymal infiltration is usually unsuitable for solid organ transplantation.

Having ascertained that the pancreas will be suitable for transplant, the surgeon will then proceed to procure the organ. Aortic perfusion only with University of Wisconsin (UW) Solution is recommended when the pancreas is being retrieved. For decontamination of the duodenal segment, which is retrieved with the pancreas, some centres recommend the use of iodine-based solution such as Betadine® down nasogastric tubes.

The superior mesenteric artery (SMA) is separated from the aorta with a small rim of aortic patch if possible. This should be done carefully, particularly if kidney retrieval is also contemplated, as the origins of renal arteries are in close proximity. If the origins of renal arteries are too close, then some surgeons advocate taking the SMA without an aortic patch.

The proximal jejunum is transected after mobilisation by dividing the ligament of Treitz with a surgical stapling device. The distal pylorus is then dissected and transected with the stapling device.

The mesentery is divided very close to the small bowel and as distant from the pancreas as possible. This is to avoid damage to the superior pancreaticoduodenal vessels. Preserving the inferior pancreaticoduodenal artery (IPA) is mandatory since this is the only artery perfusing the head and part of the uncinate process of the pancreas. An injury to the IPA would render the graft unsuitable for transplant. It is also recommended that the gastroduodenal artery (GDA) is preserved and marked with suture in case full revascularisation is required at the recipient site (e.g., when there is possible damage to IPA or in nonheart beating donor transplants). Some surgeons prefer full revascularisation and hence obtaining the SMA with a patch will be preferred.

The pancreatic head and tail are carefully mobilised from the retroperitoneum. The spleen and duodenum can be used as "handles" to lift the mobilised pancreas, minimising handling of pancreatic tissue, which could cause to graft pancreatitis. Usually there is very thin plane behind the pancreas. This plane must be strictly followed because any deviation from it can lead to damage to the splenic vein (SV) or the left renal vein.

Once removed, the pancreas is placed on cold icy slush on the back table for further preparation. The pancreas is assessed for adequate perfusion, pathological changes and iatrogenic damage. At this point, splenic tissue is also taken for tissue typing.

The splenic artery (SA) and gastroduodenal artery (GDA) are marked with fine sutures. The splenic artery may also be flushed at this point. The pancreas is kept in

fresh UW solution, removing all air from bag, packed and placed on ice in an ice box for transportation.

Allocation

Although usually simultaneously transplanted, there are two independent allocation schemes for pancreas and kidney transplants in the UK—the Pancreas Allocation Scheme and the Kidney Allocation Scheme. The UK Transplant Duty Office will use the two lists to co-ordinate the offering process. Pancreata (from both heart and nonheart beating donors) are allocated nationally based on a scoring system (Total Points Score, TPS) for both islet and the whole organ pancreas transplants.

The TPS is based on a combination of donor, recipient and transplant factors. It is a cumulative score taking into account total HLA mismatch, waiting time, sensitisation, travel time, donor body mass index (BMI), recipient dialysis status and donor to recipient age match. Recipient scores and ranking positions will therefore vary for each given donor.

PANCREAS TRANSPLANT PROCEDURE

Once potentially suitable recipients have been identified through TPS, the retrieved pancreas is ready to be transplanted. As the time period between retrieval and implantation needs to be kept to a minimum, it is not uncommon to admit more than one recipient; one as a first choice, and one as a back up, should the first choice not be suitable.

Like kidneys, pancreas allografts do not tolerate cold-ischaemia (nonperfusion time). Therefore all the effort should be made to revascularise pancreas through implantation. This should ideally be within 12 hours from the time of cross-clamping at procurement.

Back-Bench Preparation of the Pancreas Prior to Implantation

The suitability of the pancreas depends not only on the examination of the organ at the time of procurement but also at the time of reconstruction. Bench preparation of the pancreas is done in the base hospital, and is a complex surgical procedure that may take 2-3 hours. There are a number of key steps:

- Careful preparation of the portal vein to ensure that it is undamaged and long enough to facilitate the anastamosis.
- Careful examination of the whole gland from head to tail, ligating all vessels that may not have been secured at the time of retrieval. This may include ligation of all the superior mesenteric vessels as they appear below the uncinate process of the pancreas.
- Trimming of the duodenal segment taking care not to damage pancreaticoduodenal vessels that may compromise the vascular supply of the duodenum. The duodenal ends are secured with an enteric stapler and then oversewn by hand.
- Removal of the spleen and ligation of splenic vessels.
- Reconstruction of the donor splenic (SA) and superior mesenteric arteries (SMA) using an arterial conduit from the donor that comprises common, internal, and external iliac vessels as a single Y-graft.

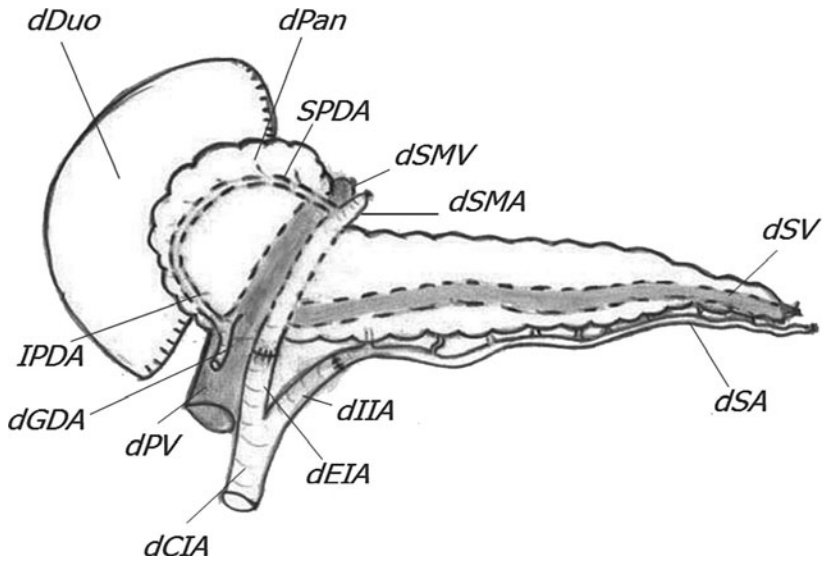

Figure 1. Pancreas, duodenum, and vessels procured from the donor and prepared for implantation. Donor pancreas (dPan), c-loop of duodenum (dDuo), splenic vein (dSV), superior mesenteric vein (dSMV), portal vein (dPV), superior mesenteric artery (dSMA), donor gastroduodenal artery (dGDA), inferior pancreaticoduodenal artery (IPDA), superior pancreaticoduodenal artery (SPDA), splenic artery (dSA), and Y-graft comprising common iliac artery (dCIA), external iliac artery (dEIA), internal iliac artery (dIIA).

- In selected cases (especially in pancreata from a nonheart-beating donor, the reconstruction may include revascularisation and anastomosis of GDA in addition to revascularisation of the above anastomoses.

Figure 1 illustrates the procured pancreas, duodenum and vessels, prepared for implantation.

The Implantation Procedure

A midline laparotomy is the preferred incision choice. The native pancreas is not removed.

Pancreas graft arterial revascularisation is usually established using the recipient right common or external iliac artery. The Y-graft described above is anastomosed end-to-side to either the patient's external or common iliac artery (Fig. 2). Positioning of the head of the pancreas graft either cephalad (head up) or caudad (head down) is not relevant with respect to successful arterial revascularisation, but may facilitate drainage of exocrine secretions which will be discussed below.

Venous drainage can either be systemic (through anastomosis to common iliac vein or distal inferior vena cava) or portal (through anastomosis to portal venous system). Currently, about 85% of pancreas transplants are performed with systemic venous drainage.

Pancreatic exocrine drainage can either be to bladder or bowel (enteric) through anastomosis of the donor duodenal segment to either the bladder or small intestine respectively (Figs. 2 and 3). Bladder-drained pancreas transplantation technique was

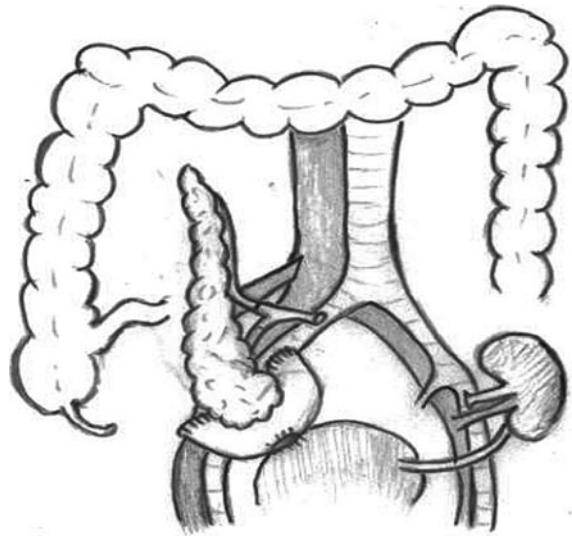

Figure 2. Bladder drained pancreas. The donor duodenal segment is anastomosed to the bladder. The donor common iliac artery is anastomosed to the recipient right common iliac artery and the donor portal vein is anastomosed to the recipient inferior vena cava (systemic drainage). Note the transplanted kidney in the left iliac fossa.

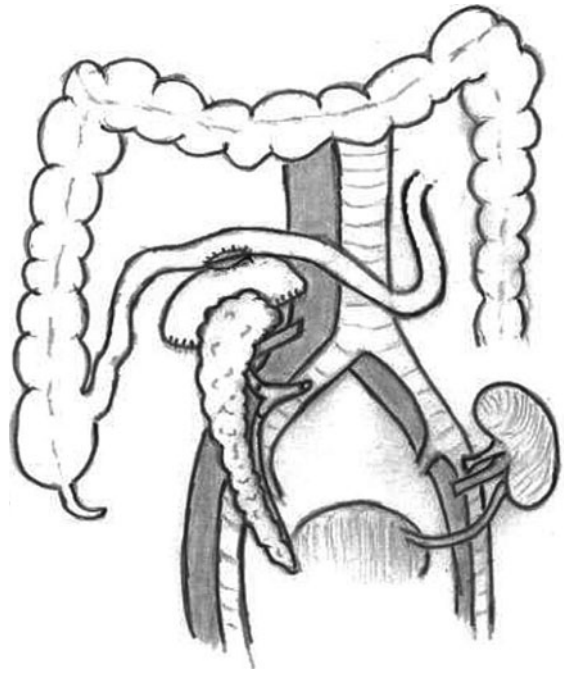

Figure 3. Enteric-drainage of pancreatic secretions. The donor duodenum loop is anastomosed to small bowel. The donor common iliac artery is anastomosed to the recipient right common iliac artery and the donor portal vein is anastomosed to the recipient inferior vena cava (systemic drainage).

an important modification first reported in 1987,[12] and was once the most common technique for managing the exocrine secretions of pancreaticoduodenal grafts.[13] However, exocrine bladder drainage has been associated with higher incidences of urinary tract infections, cystitis, urethritis, uretheral injury, balanitis, haematuria and metabolic acidosis.[14] There is a considerable conversion rate (of up to 50%) to enteric drainage, necessitating a second operation.[4,13,15] The high rate of conversion, and the advent of new immunosuppressive agents have seen enteric drainage grow in popularity. Currently, about 80% of pancreas transplantations are performed with enteric drainage.[16]

Enteric drainage is more physiological as the pancreatic enzymes are diverted into the intestines for re-absorption. Enteric drained pancreata can be constructed with or without a Roux-en-Y and the anastamosis can be made either side-to-side or end-to-side with the duodenal segment of the pancreas.

Bladder drainage however, may still be indicated in the following circumstances:

- When the recipient has a long previous history of peritoneal dialysis, and where there is significant peritoneal sclerosis.
- When there is anxiety about the vascularity of the duodenum after revascularisation as prognosis of duodeno-urinary leak is far better than enteric anastomosis leak.

Caudad positioning of the pancreatic head facilitates anastomosis for bladder drainage. In our practice, amphotericine intra-abdominal lavage following implantation of the pancreas, has been shown to reduce the rate of intra abdominal sepsis and wound infection.

In SPK, the pancreas is usually implanted first. The kidney is usually transplanted in the contralateral side. It is not uncommon for the kidney to be placed in an extra-peritoneal location by preparing a plane between the parietal peritoneum and transverse fascia. Because mobilisation of the left iliac vessels medial to the sigmoid colon is somewhat more challenging as the left iliac vessels are deeper than the right, some surgeons opt to transplant the kidney on the ipsilateral side.

POST-OPERATIVE MANAGEMENT OF THE RECIPIENT

Inpatient Care

Post operatively the recipient is usually cared for in Intensive Care Unit, High Dependency Unit or Transplant Ward. The in-patient's stay is usually between 7 and 21 days.

Immunosuppression

All pancreas transplant recipients will require life-long immunosuppression therapy to prevent rejection. There is no consensus as to the single best immunosuppressive protocol, with differing protocols adopted by individual transplant units. The underlying goals are similar, with all protocols generally aiming to prevent organ rejection, balanced against the occurrence of drug toxicity, malignancy and infection.

Two broad classifications of immunosuppressive agents exist:

- Anti-T-cell antibody induction agents
- Maintenance immunotherapy agents

The immunosuppressive regimen currently used in our unit comprises; Alemtuzumab 30 mg (Campath®) subcutaneous injection at induction, accompanied by 500 mg IV methylprednisolone. The second dose of Campath® is given on the first post-operative day 24 hours post transplant. For patients 60 years or over, a single dose of 30 mg (Campath®) subcutaneous injection at induction is adequate.

Maintenance of immunosuppression in the early post-operative period is a steroid avoidance regime and consists of intravenous cyclosporin 1 mg/kg twice a day and intravenous mycophenolate mofetil 500 mg three times a day without steroids. As soon as enteral absorption becomes possible, these are converted to oral tacrolimus 0.05 mg/kg twice daily and mycophenolic acid 540 mg twice daily.

Acute rejection episodes are treated methyprednisolone, with antithymocyte globulin (ATG) reserved for cases of steroid-resistant rejection.

Fluid Management

In the early post-operative period, fluid and electrolyte balance, cardiac parameters and metabolic function are closely monitored. Fluid volume depletion can occur rapidly due to fluid shifts, brisk diuresis, gastroparesis, and in patients with the bladder-diversion technique, loss of pancreatic fluid into the bladder. Initially, urine output, nasogastric drainage and wound drainage are measured hourly and hemodynamic assessment is done every 1-2 hours. While hospitalized, weight, heart rate, and blood pressure (standing and recumbent) are measured daily.

Hyper-/Hypoglycaemia

In the initial postoperative period, blood glucose is monitored frequently (every 2-4 hours) to assess pancreatic endocrine function. Insulin may be administered postoperatively according to a sliding scale, but is generally not required since blood glucose levels approach normal values within 12-24 hours and normalise within several days after transplantation. It is someitmes preferable to stop or avoid insulin administration and monitor blood glucose as an acute rise in blood glucose and need for insulin may signify underlying pancreas thrombosis, a complication discussed below.

Anticoagulation

Many centres have adopted a protocol for anticoagulation after pancreatic transplantation. Thromboelastography (TEG)-directed anticoagulation protocol has demonstrated that only about one-third of the patients undergoing pancreas transplantation require therapeutic anticoagulation to prevent the occurrence of graft thrombosis with the majority kept on antithrombotic prophylaxis (subcutaneous heparin and low-dose aspirin).[17] At out unit, nonfractionated heparin in combination with aspirin is used for thrombosis propylaxis.

Diet

Patients with enterically-drained pancreas are commenced on total parenteral nutrition (TPN) from the first post-operative day until signs of restored bowel activity (for instance first bowel movement) are seen. Bladder-drained patients are not commenced on TPN. In our unit, all transplant patients receive specialist input from dieticians. Following successful pancreas transplantation and restoration of normoglycaemic state, no dietary restrictions are generally required.

Patient Education

During hospitalization, transplant recipients are prepared for discharge with respect to expectations of medical compliance, education about the pharmacology of their new immunosuppressive medications, and lifestyle issues. Patients may be provided with a booklet providing them with information on these topics. In general, patients may resume normal physical activity, but are advised against participation in contact sports, to prevent direct trauma to the transplanted organs.

Outpatient Care

Once discharged, patients will be followed up in transplant clinic initially 2-3 times a week. This is gradually decreased to monthly visits in the 3rd to 6th post-operative month and then every 2-3 months through the first year. Extra-regional patients are usually referred back early to their local renal or diabetes team. This is due to the distances these patients may have to travel. However, patients may remain in extra-regional clinics for longer if there are particular surgical concerns.

Typical laboratory evaluation, obtained at some outpatient clinical encounters, includes full blood count, electrolytes, urea, creatinine, glucose, serum amylase, CRP and immunosuppression blood levels (if transplantation recipient is receiving cyclosporine, tacrolimus, or sirolimus). All pancreatic transplant recipients should have $HbA1_C$ levels done at each visit.

COMPLICATIONS OF PANCREATIC TRANSPLANTATION

Complications following pancreas transplantation can broadly be divided into four subsets:

- Parenchymal
  - Rejection
  - Pancreatitis
- Exocrine leaks and fistulation
- Vascular
  - Thrombosis
  - Hemorrhage
  - Pseudoaneurysm and arteriovenous fistula

- Peripancreatic
  - Lymphocoele
  - Abscess
  - Haematoma
  - Pseudocyst
  - Urinoma
- Bowel obstruction
- Systemic complications

Parenchymal Complications

Graft Pancreatitis

As a result of cold-ischaemia time, organ handling and organ reperfusion, pancreatitis occurs to some degree in all patients. This is usually mild and self-limiting, but a small subset of patients may experience severe pancreatitis following surgery with resultant threat to graft survival. Pancreatitis occurring weeks after surgery may be secondary to reflux of exocrine secretions ("reflux pancreatitis").

Pancreatitis may manifest as elevated amylase, pyrexia, tenderness over graft site and elevated amylase. As seen in native pancreatitis, the inflammatory process around the transplanted pancreas can result in pseudocyst formation, abscesses, vascular thrombosis and pseudoaneurysm.

Graft Rejection

Acute graft rejection (Fig. 4) has been reported to complicate up to 10.6% of pancreatic transplants.[18] The process is thought to be the result of an alloimmune

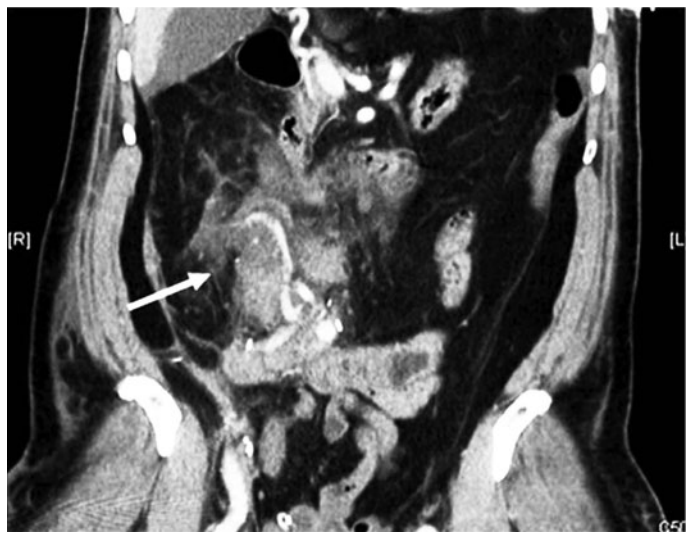

Figure 4. Abdominal CT coronal reformat depicts inflammatory stranding around the transplanted pancreas sited in the right iliac fossa (white arrow) in keeping with pancreatitis.

arteritis causing small and subsequently more proximal, larger vessel occlusion.[19] Following multiple episodes of acute rejection, the graft may eventually be small and atrophic, and chronic rejection is established. Acute rejection has been reported to be more common among cytomegalovirus (CMV) infected patients (66 vs. 41% without infection).[20]

Graft rejection may manifest as low-grade pyrexia, unexplained elevated white cell count, and graft site tenderness. Alterations in C-peptide and insulin levels may not be present in early acute rejection.

Exocrine Leak

Leakage of exocrine secretions occurs in up to 10% of transplant patients following enteric drainage and is a significant cause of graft loss.[21] The nature and constitution of pancreatic exocrine secretions can incite strong inflammatory intraperitoneal responses, with resultant formation of phlegmons, infected collections or fistulae.

Leaks in the early-post-operative period are usually related to ischemia or anastomotic techniques. In the later post-operative period, infection, rejection, and duodenal staple line ischaemia are usually incriminated.

As a result of immunosuppressive therapy, some transplant patients may not display signs of infection or leak, and a high index of suspicion is critical to timely diagnosis and intervention. Treatment usually takes the form of surgical repair and whilst clinical suspicion may be sufficient to mandate treatment, imaging in the form of cross-sectional imaging can often provide confirmatory evidence in equivocal cases.

Graft Thrombosis

Pancreas graft loss due to venous thrombosis is the leading non-immunological cause for graft failure following kidney-pancreas transplantation. Pancreas thrombosis occurs in 12-13% of pancreas transplants,[22,23] usually within 24 hours but may occur up to 4 days after transplant.

Thrombosis can be venous or arterial, with the former being more common. In most patients, graft thromboses occur early after transplant and should be suspected in the setting of graft tenderness, hyperglycaemia, elevated serum amylase or lipase. A decrease in urinary amylase may also be seen in patients with bladder drainage.

Donor (older age and cerebrovascular cause of death) and surgical factors (low blood flow within the pancreas graft, cold ischemia time in excess of twelve hours, left-sided implantation into recipient, and use of an inter-positioned vascular graft) have been reported to be associated with graft thrombosis.[4,22]

CT (Fig. 5) and conventional angiography may be used in the evaluation of patients with suspected graft thrombosis, but will usually require intravenous iodinated contrast, which may be detrimental in the setting of recovering renal insufficiency following SPK transplants. Small studies of magnetic resonance (MR) angiography have shown promising results in the diagnosis of graft thrombosis.[24,25]

Complete arterial or venous thrombosis are usually not salvageable conditions and often require re-exploration and pancreatectomy for treatment. However, systemic anticoagulation, percutaneous thrombolysis or thrombectomy have been performed in selected cases of partial thrombosis.[23]

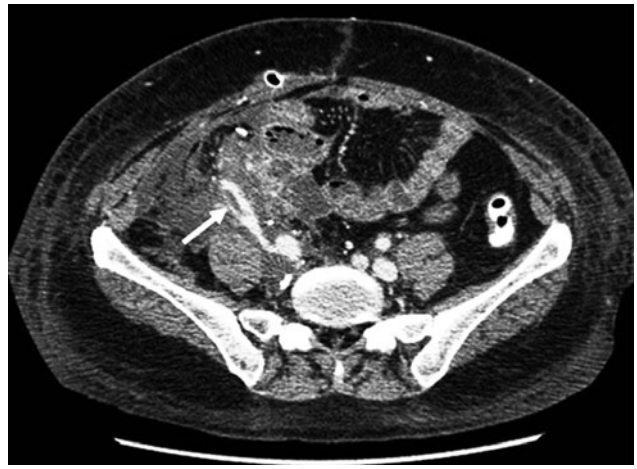

Figure 5. Abdominal CT in a post-transplant recipient depicts a linear filling defect within the donor portal vein (white arrow) consistent with thrombosis. There is also peripanreatic fluid and stranding from graft pancreatitis.

Haemorrhage

Bleeding in the early-post-operative period is usually due to surgical factors. Duodenal segment ischaemia or ulceration are usually secondary to CMV infection and may cause bleeding into the gastrointestinal tract.

Haemorrhage should be suspected in the context of decreasing haematrocrit or haemoglobin levels. Haematuria in bladder-drained patients can be evaluated using cystoscopy, but bleeding in enteric-drained patients may be more difficult to visualise. Upper and lower gastrointestinal endoscopy, small bowel follow-through, cross-sectional imaging or nuclear medicine studies in the form of Tc-99m-labelled red blood cells may be used in enterically-drained patients to establish presence of gastrointestinal blood and identify site of bleeding.[26,27] Catheter angiography is a technique which may be used to both diagnose and treat bleeding (though embolisation of bleeding vessel), potentially sparing the patient from graft pancreatectomy.

Aneurysms and pseudoaneurysms of the donor arteries are relatively rare and may present with haemorrhage. These may be idiopathic or be the sequelae of graft pancreatitis or infection (mycotic aneurysms).[28-31] Unexplained intra-abdominal bleeding in a patient with a history of abdominal abscess should raise the possibility of a pseudoaneurysm. In patients with pseudoaneurysms, catheter angiography affords both diagnostic and therapeutic capabilities. Coil embolisations of pseudonaneurysms have been performed with good results.[31]

Peripancreatic Collections

In the early post-operative period, fluid collections around the graft pancreas are common and are associated with increased morbidity, mortality and graft loss.[32,32] Fluid collections include urinoma, seroma, lymphocele, abscess, hematoma and pseudocyst.

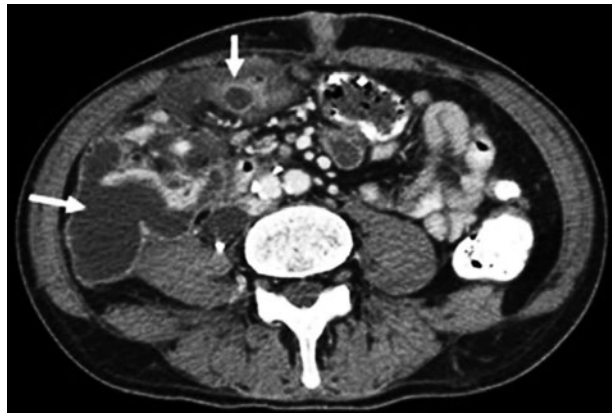

Figure 6. Abdominal CT in a patient post-pancreatic transplantation depicts rim-enhancing collections (white arrows) in the right iliac fossa, near the transplant pancreas.

Ultrasound and cross-sectional imaging (Fig. 6) can be used to detect presence of and define the extent of the collection, but the determination of fluid composition may require diagnostic fluid aspiration.

Bowel Obstruction

In the lateral post-operative period, bowel obstruction following transplant can occur as a consequence of adhesions. Internal herniation through a defect created at the time or intraperitoneal placement of the pancreatic allograft may also result in bowel strangulation and obstruction.[33]

Systemic Complications

Patients on immunosuppressants are exposed to increased risk of infection by viruses, bacteria and fungi. As with all immunosuppressed transplant patients, cytomegalovirus (CMV) infection is common, occurring in up to 34% of SPK patients. Acute rejection has been reported to be more common among CMV-infected patients (66%) versus (41%) without infection.

As discussed previously, metabolic disturbances can occur, particularly in bladder-drained patients,[14] secondary to loss of bicarbonate-rich pancreatic secretions into the urine. Metabolic acidosis and hypovolaemia may ensue. Therefore, most pancreas recipients with bladder drainage will require long term sodium bicarbonate supplementation.

Post-transplant malignancy is recognised as being a major limitation to the success of solid organ transplantation and it is currently considered one of the unavoidable costs of long-term immunosuppressive therapy. The incidence of malignancy is elevated in solid organ transplant recipients and has been estimated at 20% after 10 years of chronic immunosuppression.[34] There appears to be a relationship between immunosuppressive therapy and posttransplant malignancy, with epidemiological data revealing that the length of exposure to immunosuppressive therapy and the intensity of therapy are clearly related to the posttransplant risk of malignancy, and that once cancer has

developed, more intense immunosuppression can translate into more aggressive tumour progression in terms of accelerated growth and metastasis.[35] The pathogenesis is thought to result from impaired cancer surveillance and facilitation of oncogenic viruses from immunosuppressive therapy.

Post-transplant lymphoproliferative disorder (PTLD) is a significant cause of morbidity and has been reported in 2.4-6.1% of patients following pancreatic transplant.[36,37] On cross-sectional imaging, lymph nodal enlargement and lesions within the liver, spleen, kidney, gallbladder or bowel may be seen.[38] The pancreatic allograft itself can be diffusely enlarged, an appearance that may be indistinguishable radiologically from acute pancreatitis or transplant rejection. However, failure of response to immunosuppressive therapy and the presence of intra- or extra-allograft focal masses should suggest the diagnosis of PTLD.[37]

ISLET CELL TRANSPLANT

Islet cell transplant is emerging as an alternative means of restoring endogenous insulin secretion. Overall, 70% of all islet-alone recipients achieved insulin independence[39] compared with 85% graft survival rate at 1-year in SPK patients,[40] but insulin independence in islet-cell recipients is not usually sustainable in the longer-term. A five-year study of 65 Type 1 diabetes patients treated with islet transplants showed that 72.3% achieved insulin independence, but with only 10% remaining insulin independent after five years. The median duration of insulin independence was 15 months. However, 80 percent had C-peptide secretion, required less pretransplant dose of insulin, and demonstrated more glucose level stability than prior to islet-cell treatment.[41] In another multicenter study of 36 Type 1 diabetic patients treated with islet cell transplantation,[42] 16 (44%) met the primary end point of insulin independence at one year. A total of 21 patients (58%) attained insulin independence with good glycaemic control at any point throughout the trial. Of these, 16 (76%) required insulin again at 2 years; with the remaining 5 remaining insulin-independent at 2 years.

Like whole organ transplantation, there are three main types of islet cell transplantation procedures:

- Simultaneous islet-kidney transplantation (SIK)
- Islet after kidney transplantation (IAK)
- Islet transplantation alone (ITA).

Islet cell transplantation requires initial isolation and processing of donor pancreata. Transplantation technique (Fig. 7) involves a percutaneous catheter that is introduced into the liver and advanced retrogradely under fluoroscopic and/or ultrasound guidance into the portal vein of the recipient. The processed pancreata is then injected into the portal vein.

Complications that can occur following islet cell transplantation include intraperitoneal bleeding (which may necessitate transfusion or laparotomy), portal vein thrombosis, hypercholesterolemia and adverse events related to immunosuppresion.[42,43]

CONCLUSION

Whole organ pancreatic transplantation is a viable treatment option for diabetes mellitus. However, it involves a major surgical procedure and the benefits of the procedure

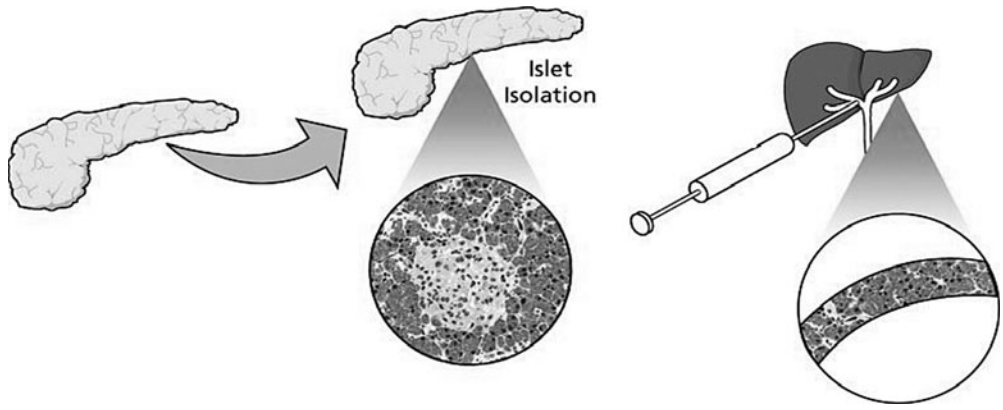

Figure 7. Islet cell transplant. Islet cells are isolated from the donor pancreas. Following processing, the pancreata is injected into the portal vein under fluoroscopic and/or sonograhic guidance.

have to be weighed against the risks. Transplantation of islet cells is an alternative to the whole organ pancreas transplantation. However, this treatments has its own value and negative after effects.

REFERENCES

1. Kelly WD, Lillehei RC, Merkel FK et al. Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy. Surgery 1967; 61(6):827-837.
2. Perosa M, Boggi U, Cantarovich D et al. Pancreas transplantation outside the USA: An update. Curr Opin Organ Transplant 2011.
3. Reddy KS, Stablein D, Taranto S et al. Long-term survival following simultaneous kidney-pancreas transplantation versus kidney transplantation alone in patients with type 1 diabetes mellitus and renal failure. Am J Kidney Dis 2003; 41(2):464-470.
4. Sollinger HW, Odorico JS, Becker YT et al. One thousand simultaneous pancreas-kidney transplants at a single center with 22-year follow-up. Ann Surg 2009; 250(4):618-30
5. Morath C, Zeier M, Dohler B et al. Transplantation of the type 1 diabetic patient: The long-term benefit of a functioning pancreas allograft. Clin J Am Soc Nephrol 2010; 5(3):549-552.
6. Navarro X, Sutherland DE, Kennedy WR. Long-term effects of pancreatic transplantation on diabetic neuropathy. Ann Neurol 1997; 42(5):727-736.
7. Giannarelli R, Coppelli A, Sartini MS et al. Pancreas transplant alone has beneficial effects on retinopathy in type 1 diabetic patients. Diabetologia 2006; 49(12):2977-2982.
8. Fioretto P, Steffes MW, Sutherland DE et al. Reversal of lesions of diabetic nephropathy after pancreas transplantation. N Engl J Med 1998; 339(2):69-75.
9. White SA, Shaw JA, Sutherland DE. Pancreas transplantation. Lancet 2009; 373(9677):1808-1817.
10. Kaufman DB. Pancreas transplantation clinical presentation. Medscape Reference [serial on internet]. 2011 March 16. Available from http://emedicine.medscape.com/article/429408-clinical.
11. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). National diabetes statistics, 2011. Bethesda: National Institutes of Health; 2011 February. Available from http://diabetes.niddk.nih.gov/dm/pubs/statistics/2011.
12. Nghiem DD, Corry RJ. Technique of simultaneous renal pancreatoduodenal transplantation with urinary drainage of pancreatic secretion. Am J Surg 1987; 153(4):405-406.
13. West M, Gruessner AC, Metrakos P et al. Conversion from bladder to enteric drainage after pancreaticoduodenal transplantations. Surgery 1998; 124(5):883-893.
14. Monroy-Cuadros M, Salazar A, Yilmaz S et al. Bladder vs enteric drainage in simultaneous pancreas-kidney transplantation. Nephrol Dial Transplant 2006; 21(2):483-487.

15. Jimenez-Romero C, Manrique A, Morales JM et al. Conversion from bladder to enteric drainage for complications after pancreas transplantation. Transplant Proc 2009; 41(6):2469-2471.
16. Gruessner AC, Sutherland DE. Pancreas transplant outcomes for united states (US) and non-US cases as reported to the united network for organ sharing (UNOS) and the international pancreas transplant registry (IPTR) as of june 2004. Clin Transplant 2005; 19(4):433-455.
17. Vaidya A, Muthusamy AS, Hadjianastassiou VG et al. Simultaneous pancreas—kidney transplantation: To anticoagulate or not? is that a question? Clin Transplant 2007; 21(4):554-557.
18. Larson TS, Bohorquez H, Rea DJ et al. Pancreas-after-kidney transplantation: An increasingly attractive alternative to simultaneous pancreas-kidney transplantation. Transplantation 2004; 77(6):838-843.
19. Dobos N, Roberts DA, Insko EK et al. Contrast-enhanced MR angiography for evaluation of vascular complications of the pancreatic transplant. Radiographics 2005; 25(3):687-695.
20. Ricart MJ, Malaise J, Moreno A et al. Cytomegalovirus: Occurrence, severity, and effect on graft survival in simultaneous pancreas-kidney transplantation. Nephrol Dial Transplant 2005; 20(Suppl 2):ii25-32, ii62.
21. Goodman J, Becker YT. Pancreas surgical complications. Curr Opin Organ Transplant 2009; 14(1):85-89.
22. Troppmann C, Gruessner AC, Benedetti E et al. Vascular graft thrombosis after pancreatic transplantation: Univariate and multivariate operative and non-operative risk factor analysis. J Am Coll Surg 1996; 182(4):285-316.
23. Gilabert R, Fernandez-Cruz L, Real MI et al. Treatment and outcome of pancreatic venous graft thrombosis after kidney—pancreas transplantation. Br J Surg 2002; 89(3):355-360.
24. Hagspiel KD, Nandalur K, Pruett TL et al. Evaluation of vascular complications of pancreas transplantation with high-spatial-resolution contrast-enhanced MR angiography. Radiology 2007; 242(2):590-599.
25. Eubank WB, Schmiedl UP, Levy AE et al. Venous thrombosis and occlusion after pancreas transplantation: Evaluation with breath-hold gadolinium-enhanced three-dimensional MR imaging. AJR Am J Roentgenol 2000; 175(2):381-385.
26. Barone GW, Webb JW, Hudec WA. The enteric drained pancreas transplant: Another potential source of gastrointestinal bleeding. Am J Gastroenterol 1998; 93(8):1369-1371.
27. Bingener-Casey J, Esterl RM Jr, Kenneth Washburn W et al. Tc-99m-labeled red blood cell scanning localizes anastomotic hemorrhage between the distal ileum and duodenal stump of an enteric-drained pancreas transplant. Clin Nucl Med 2002; 27(3):205-206.
28. Green BT, Tuttle-Newhall J, Suhocki P et al. Massive gastrointestinal hemorrhage due to rupture of a donor pancreatic artery pseudoaneurysm in a pancreas transplant patient. Clin Transplant 2004; 18(1):108-111.
29. Verni MP, Leone JP, DeRoover A. Pseudoaneurysm of the Y-graft/iliac artery anastomosis following pancreas transplantation: A case report and review of the literature. Clin Transplant 2001; 15(1):72-76.
30. Tzakis AG, Carroll PB, Gordon RD et al. Arterial mycotic aneurysm and rupture. A potentially fatal complication of pancreas transplantation in diabetes mellitus. Arch Surg 1989; 124(6):660-661.
31. Dalla Valle R, Capocasale E, Mazzoni MP et al. Embolization of a ruptured pseudoaneurysm with massive hemorrhage following pancreas transplantation: A case report. Transplant Proc 2005; 37(5):2275-2277.
32. Patel BK, Garvin PJ, Aridge DL et al. Fluid collections developing after pancreatic transplantation: Radiologic evaluation and intervention. Radiology 1991; 181(1):215-220.
33. Lall CG, Sandrasegaran K, Maglinte DT et al. Bowel complications seen on CT after pancreas transplantation with enteric drainage. AJR Am J Roentgenol 2006; 187(5):1288-1295.
34. Kapoor A. Malignancy in kidney transplant recipients. Drugs 2008; 68 Suppl 1:11-19.
35. Gutierrez-Dalmau A, Campistol JM. Immunosuppressive therapy and malignancy in organ transplant recipients: A systematic review. Drugs 2007; 67(8):1167-1198.
36. Issa N, Amer H, Dean PG et al. Posttransplant lymphoproliferative disorder following pancreas transplantation. Am J Transplant 2009; 9(8):1894-1902.
37. Meador TL, Krebs TL, Cheong JJ et al. Imaging features of posttransplantation lymphoproliferative disorder in pancreas transplant recipients. AJR Am J Roentgenol 2000; 174(1):121-124.
38. Pickhardt PJ, Siegel MJ. Posttransplantation lymphoproliferative disorder of the abdomen: CT evaluation in 51 patients. Radiology 1999; 213(1):73-78.
39. Collaborative Islet Transplant Registry (CITR). Collaborative islet transplant registry (CITR) 2009 report. www.citregistry.org. Accessed, 2011.
40. The US Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients COPTN/SRTR. Annual report: transplant data 1999-2008. http://optn.transplant.hrsa.gov/ar2009/chapter_III_AR_CD.htm?cp=4#2. Accessed, 2011.
41. Ryan EA, Paty BW, Senior PA et al. Five-year follow-up after clinical islet transplantation. Diabetes 2005; 54(7):2060-2069.
42. Shapiro AM, Ricordi C, Hering BJ et al. International trial of the edmonton protocol for islet transplantation. N Engl J Med 2006; 355(13):1318-1330.
43. Ryan EA, Lakey JR, Paty BW et al. Successful islet transplantation: Continued insulin reserve provides long-term glycemic control. Diabetes 2002; 51(7):2148-2157.