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Kidney-Pancreas Transplantation

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1. Introduction

During the past decade, simultaneous pancreas kidney transplantation has been widely accepted as the most effective way to achieve normoglycemia in patients with type 1 diabetes and end-stage renal disease. This procedure was performed for the first time on a human in 1966 but it was in the 1980s, with advances in surgical technique and introduction of cyclosporine for immunosuppression, that the success rates of SPK became acceptable. According to international pancreas transplant (IPTR) report as of December 31, 2004, 23,043 pancreas transplants were performed worldwide. These included more than 17,000 (17,127) performed in the United States (US) and nearly 6,000 (5,916) from outside the US (non-US). In the US, the majority of the cases, 78% (n=11,898), have been simultaneous pancreas-kidney transplants (SPK); 16% (n=2427) are pancreas after kidney (PAK) transplants; 7% (n=1,008) are pancreas transplants alone (PTA).

Indications for pancreas transplantation include the development of diabetic complications such as ESRD, retinopathy or multiple attacks of hypoglycemic unawareness. Unfortunately, pancreas transplantation has been associated with the highest surgical complication rate of all the routinely performed organ transplant procedures (except for small intestinal or multivisceral transplantation) and the risk of pancreas graft loss from surgical complications (technical failures) is higher than from immunological reasons. The overall incidence of surgical complications in PTx is reported to be around 10% to 38%. This high rate of complications leads US centers to preclude PTA in most centers and now over 95% of pancreas transplantations are performed in patients with renal disease or a previous functioning kidney transplant. One year patient, kidney, and pancreas survival rates for recipients of an SPK transplant are 95%, 91%, and 86%, respectively. Compared to patients with diabetes who receive a kidney alone, the addition of a pancreas improves long-term patient and kidney graft survival. Recipients of a pancreas-after-kidney transplant or a pancreas transplant alone have an average 1-year pancreas graft survival rate of 78-83%.

In this chapter we will thoroughly describe many aspects of this complex transplantation procedure including:

- The history of pancreas transplantation
- Indications for pancreas transplantation
- Surgical aspects of pancreas graft procurement from the deceased donor
- Current surgical techniques for pancreas transplantation
- Immunosuppressive regimens

- Postoperative care of pancreas transplant recipients
- Complications of pancreas transplantation
- Long term results of pancreas transplantation

2. History of pancreas transplantation

Experimental transplantation of the pancreas in animals began as early as 1890 with proved success in the treatment of insulin dependent diabetes mellitus (Burke GW , et al, 2004). Grafting 3 pieces of sheep pancreas into the subcutaneous tissue of a diabetic child by Williams in 1893 was another attempt to treat diabetes but the patient died after 3 days because of severe ketoacidosis (Williams PW, 1903). The first clinical attempt to cure type 1 diabetes by vascular pancreas transplantation was done simultaneously with kidney transplantation, at the University of Minnesota in 1966 three years after first successful kidney transplantation (Kelly WD, et al, 1967), but the procedure was not performed with any frequency until many years later. Only 12 cases were done between 1967 till 1973 at the same center but almost all of them rejected before the first year after the operation. Segmental pancreas transplantation from living donors first introduced in 1979. Besides the rejection and vascular problems, dealing with pancreas exocrine secretion was complicated this type of procedure from the early days. By the mid-70s three different techniques were in use: enteric drainage, urinary drainage (into the ureter or directly into the bladder and duct injection. Ureteral drainage was first introduced by Gleidman et al (Gleidman et al , 1973). Bladder drainage first by direct anastomosis of the pancreatic duct to the bladder by Sollinger et al (Sollinger HW, et al, 1984) and then by duodenocystostomy by Nghiem and Corry (Nghiem DD & Corry RJ, 1987) was the most common method for exocrine drainage during the 1980s and 1990s and was still in use in some centers around the world specially for solitary pancreas transplantation. In the early 80's, a dramatic improvement in outcomes happened due to introduction of cyclosporine for immunosuppression (Squifflet JP, et al, 2008). In 1984, Starzl et al (Starzl et al,1984) reintroduced the technique of enteric drainage as originally described by Lillehei which is now is the routine procedure in most pancreas transplant centers.

In 1992, systemic venous drainage which was done through anastomosis of the portal vein to recipient iliac veins was replaced by direct portal drainage by Rosenlof et al (Rosenlof LK, et al, 1992) and also Shokouh-Amiri et al (Shokouh-Amiri MH, et al, 1992) because of its more physiologic pattern of insulin delivery. Now during the modem era of immunosuppression, the whole pancreas transplantation technique with portal - enteric drainage became the gold standard for simultaneous pancreas and kidney transplantation (SPK), and even for pancreas after kidney (PAK) or pancreas transplantation alone (PTA) and as of December 31, 2004, 23,043 pancreas transplants were reported to the international pancreas transplant registry (IPTR) of whom over 60% were performed in the united states.

3. Indications for pancreas transplantation

Patients with type 1 or insulin dependent type 2 diabetes mellitus are eligible for pancreas transplantation when they have any major complications of their disease, but because of complications of this type of surgery and need for lifetime immunosuppression therapy and frequent interventional surveillance (such as protocol biopsies), both the clinicians and the

patients should be aware of those conditions that really might benefit from pancreas transplantation. Most common indications are as follows: diabetic nephropathy, retinopathy, neuropathy, disabling or life threatening hypoglycemic unawareness or incapacitating emotional or clinical problems associated with insulin therapy (White et al, 2009). Some of the rare indications (which are not accepted by all transplant surgeons) are diabetic complications after total pancreatectomy, presence of other autoimmune diseases, insulin allergy or resistance to subcutaneous insulin.

Patients should be considered as potential candidate for pancreas transplantation only when their morbidity or mortality risk of the surgical procedure or long term immunosuppressive treatment are lower than the diabetic complications (Meloche RM, 2007). Unfortunately, most patients with chronic diabetes who develop these complications have major comorbidities such as obesity, cardiovascular, cerebrovascular or peripheral vascular diseases, diabetic gastropathy, and vascular or neuropathic diabetic foot. These patients are most suitable for pancreatic islet cell transplantation which is very simpler and has fewer and more minor complications that the relatively complex surgical procedure of whole pancreas transplantation.

Patients with diabetic nephropathy who need concomitant renal transplantation are the most common eligible patients who benefits from simultaneous kidney pancreas transplantation (SPK). Those who previously underwent kidney transplantation are candidate for pancreas after kidney (PAK) transplantation. According to 2004 annual IPTR report (The University of Minnesota, modified on May 28, 2009, available from www.iptr.umn.edu/annual_reports/2004_annual_report/3_txs_cat/home.html) pancreas transplant alone (PTA) now performed in less than 5% of all pancreas transplant recipients because unlike SPK or PAK recipients they don't otherwise need immunosuppression for their renal allograft and surgical complications of this procedure and higher rejection rate of this type of operation outweigh the potential benefits of glycemic control. PTA is best appropriate for those patients with hypoglycemic unawareness, stable renal function, and minimum proteinuria (White et al, 2009), because calcineurin inhibitor immunosuppressive therapy reduces the glomerular filtration rate at least 20% in the first year after pancreas transplantation (Mazur et al, 2004) PAK transplantation is performed mostly in patients who have an appropriate living donor for kidney graft and also are simultaneously candidate for pancreas transplantation. When coordinate logistics available, these operation using kidney graft from the living donor and pancreas graft from a deceased donor may be performed at the same time and at the same center. In some centers partial segmental pancreas transplantation technique is used for SPK when the living donor is suitable for this complex procedure firstly performed by Merkel in 1973 (Merkel et al, 1973).

The contraindications for pancreas transplantation are the same as other types of transplantations (Tiong & Krishnamurthi, 2011): active infections, coronary angiographic evidence of significant non-correctable or untreatable coronary artery disease, recent myocardial infarction, ejection fraction below 30%, history of recent, incompletely treated malignancy (excluding non-melanoma skin cancer), positive HIV serology, positive hepatitis B surface antigen serology, substance abuse, major ongoing psychiatric illness, recent history of noncompliance, inability to provide informed consent, any systemic illness that would severely limit life expectancy or compromise recovery, significant, irreversible hepatic or pulmonary dysfunction. In major pancreas transplant centers like University of Wisconsin, Minnesota, correctable (by stenting, angioplasty or bypass) coronary artery disease is not considered as a contraindication for pancreas transplantation (Sollinger HW,

et al, 2009). Most pancreas transplant programs exclude patients older than 45-50 years of age, because higher age is an independent risk factor for predicting poorer surgical outcome, although the rejection rate is significantly lower in this age group (Gruessner AC & Sutherland DE, 2005).

4. Surgical aspects of pancreas graft procurement from the deceased donor

Not all deceased donors are suitable for pancreas graft procurement. Absolute contraindications for pancreas donation are active infection or malignancy, positive serologic evaluation for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and human T cell lymphotropic virus type 1 (HTLV-1), proved diabetes mellitus, pancreatitis (acute/chronic), severe pancreatic steatosis or edema, previous pancreatic surgery and intra-abdominal sepsis. Donor hyperglycemia is common because of stress condition and use of high dose corticosteroids and not a contraindication for use of the pancreas, although it may contribute as a minor risk factor for long-term graft loss (Gores, et al, 1992). Most surgeons only select younger non-obese donors (age 10-50 years, weight 30-100 kg) who are hemodynamically stable without need to high doses of vasopressors. Also a cardiocerebrovascular cause of brain death and massive volume resuscitation are other risk factors for postoperative complications in the recipients (Troppmann C, 2004). Because of these stringent criteria, according to IPTR report, in the United States only 21% of the deceased donor pancreata were used for transplantation during the year 2004. Because pancreas transplantation is not life saving, procurement of other donor organs are more important. If the surgeon considers that the pancreas is not suitable for transplantation it may be used for research or pancreas islet cell transplantation (Shapiro, et al, 2000).

The procedure starts with a long midline incision from suprasternal notch to symphysis pubis area usually by the liver team. All intrathoracic and abdominal organs are evaluated systematically to rule out any suspicious lesion. First, all usual dissections for controlling supraceliac and infrarenal aorta, arc of thoracic aorta and superior or inferior mesenteric vein should be performed, so in case that patient becomes unstable the surgeon can rapidly proceed with cold perfusion of the organs for their safe retrieval. The right colon is completely mobilized from retroperitoneum and then an extended Kocher maneuver is done. All ligaments of the liver are transected and then arterial anatomy of the liver and pancreas is evaluated by palpating the hepatic artery pulsation in the hepatodudenal portion of lesser omentum. The surgeon should have complete knowledge of hepatic artery abnormalities and possibility of existence of a right accessory or right replaced hepatic artery that originate from superior mesenteric artery. In rare cases the entire hepatic artery are originated from superior mesenteric artery. With novel microsurgical techniques none of these anomalies is considered as a contraindication for concomitant liver, pancreas or small intestinal harvesting from a deceased donor. It's better to perform a dissection of the supraduodenal area to reveal the anatomy of common hepatic artery, gastroduodenal and celiac trunk branches specially the origin of the splenic artery. The other dissections may be performed after cold perfusion. The common bile duct is divided and infrarenal aorta and superior or inferior mesenteric vein are cannulated at the next stage. Supraceliac aorta is clamped 3-5 minutes after systemic heparinization and the heart team also clamps the aortic arc and cold perfusion is started.

The most commonly used solutions for cold perfusion are Belzer University of Wisconsin (UW), histidine - tryptophan - ketoglutarate (HTK) and Celsior solution with no significant difference in the results when cold ischemia time is less than 12 hours, but UW is the standard solution in most centers (Fridell et al, 2010).

The donor blood evacuated through the supradiaphragmatic or in some certain cases (such as history of previous thoracic surgery) infrarenal inferior vena cava (IVC). After removing the heart and lungs, liver, pancreas and small intestine usually are procured en bloc and the remaining dissection may be performed in the bench procedure. The duodenal lumen is irrigated by 500 ml of 20% Betadine, 50 mg/ml amphotericin B and metronidazole solution through the nasogastric tube and distal and proximal part are transected by gastrointestinal (GIA) staplers. The portal vein is divided 1 cm to 2 cm above the pancreas border. The gastroduodenal artery is divided and suture ligated and the splenic artery is divided close to its origin and marked by a nonabsorbable 6-0 suture for future identification. The base of mesentery at the inferior border of pancreas is transected by another GIA stapler and the whole pancreas-duodenum-spleen graft removed.

In back table or bench procedure, all excessive fat tissue and spleen should be removed and the origin of mesentery and all small arterial and venous branches in the inferior border of pancreas is reinforced again for future hemostasis. Duodenum is shortened again and reinforced in both distal and proximal side by non-absorbable sutures. Arterial reconstruction is performed by anastomosis of the donor iliac Y-graft, external and internal iliac branches to the graft superior mesenteric and splenic artery, respectively. We also recommend using a small segment of donor left gastric or inferior mesenteric artery for reperfusion of gastroduodenal artery for better circulation of duodenum and head of pancreas to prevent future frequent duodenal ulcers in the graft.

5. Current surgical techniques for pancreas transplantation

Forty five years after the first SPK, controversy continues regarding the site of both venous effluent and exocrine drainage and also many other aspects in this complex surgical procedure. In most centers, SPK is performed separately by two teams. During kidney transplant procedure, the pancreas team prepares the pancreas graft for transplantation. Usually an intraperitoneal approach is used by a long midline incision and the kidney graft is transplanted by standard technique to left iliac fossa (renal artery to internal or external iliac artery and then renal vein to external iliac vein and at last ureter to the bladder or native ureter as described in other chapters of this book). Use of right side for pancreas transplantation is recommended due to more superficial iliac artery position in this side, which makes arterial anastomosis easier. The next step is arterial or venous reconstruction. Except for a few minor changes in arterial reconstruction technique (such as reperfusion of gastroduodenal artery or changing the site of arterial inflow), there is no significant change in the arterial reconstruction technique during these era. There are at least 2 options for venous drainage: systemic or portal drainage. It's better to reconstruct the venous drainage before arterial anastomoses because a short portal vein of the graft may limit the later maneuvers needs for venous anastomosis. In our center we use the recipient superior mesenteric vein at the base of mesentery below the transverse mesocolon for venous outflow(portal drainage) and right common iliac artery for arterial inflow to the donor iliac Y-graft. Those surgeons that prefer to use systemic venous drainage use the right external or common iliac vein as the venous outflow, perfectly as the same manner that they used

external iliac artery and vein for kidney transplantation. After completing the arterial and venous anastomoses, the graft is reperfused and complete hemostasis is done. Usually despite every effort for complete hemostasis during back table preparing of the pancreas graft, there is brisk bleeding around the borders of the graft at the time of reperfusion and crystalloid and blood product replacement should be used to prevent hypotension and subsequent damage to the kidney and pancreas grafts. Graft splenectomy is done at this stage by some surgeons. The next step is anastomosis of the graft duodenum to the recipient jejunum (enteric drainage) or bladder (bladder drainage). When portal drainage is chosen, the pancreas head should be directed cephalad and use of bladder drainage is almost impossible and vice versa. In other words, if the surgeon selects bladder drainage for duct management (as is the case for most PTA surgeries), the pancreas head should be directed caudad and use of portal venous drainage won't be possible. Also if portal drainage is used we need a rather longer donor common iliac artery or even an extension graft for arterial reconstruction of the graft.

Drains are inserted at the end of operation around the kidney and pancreas graft separately to monitor for postoperative bleeding and leakages. We prefer to perform the kidney transplant operation retroperitoneally in the left iliac fossa and at the end use the peritoneum to hide the kidney to be able to monitor the kidney graft complications such a urine leakage and lymphocele s1eparately from the pancreas graft.

It is worthwhile to describe briefly about the evolution of these techniques in the leading center of pancreas transplantation in the world, University of Minnesota (Sutherland DE, 2001). For pancreas graft duct management they used many techniques during this long term period: a cutaneous graft duodenostomy, open duct free intraperitoneal drainage, duct occlusion (simple ligation or polymer-injection), enteric drainage (ED) and urinary drainage (bladder and only 4 cases to the ureter). Except for ED and bladder drainage (BD), the other techniques of duct management were used only in the early years of pancreas transplantation evolution in a small portion of their cases because of their recognized complications and now they (along with most other pancreas centers around the world) lose their early enthusiasm to BD technique because of its chronic complications such as hyperchloremic metabolic acidosis, dehydration, chemical cystitis and urethritis, recurrent hematuria, bladder stones, and recurrent graft pancreatitis, recurrent urinary tract infections, urethral stricture and perineal excoriations (Han DJ & Sutherland DE, 2010). They recommended using BD for duct management because they could monitor the graft function by serial measurement of urinary amylase and they had showed that decrease in urinary amylase always preceded hyperglycemia as a manifestation of rejection in pancreas grafts. For SPK bladder drainage transplants, monitoring of urine amylase was less important to detect rejection because a serum creatinine elevation usually preceded a urine amylase decline when the rejection episode affected both organs. In the past, severe complications would lead to conversion of BD to ED in up to 25% of patients within 10 years (Sollinger HW, et al, 1992). Enteric drainage also has many complications (at least risk of enteric contamination) that may be devastating in case of duodenal necrosis and gastrointestinal leakage.

Several options are available for enteric drainage: side-to-side duodenojejunostomy, or duodenojejunostomy with a Roux-en-Y limb and duodenoduodenostomy (Hummel et al, 2008). The site of duodenojejunostomy (distance from the Treitz ligament) and its length are different between authors. Although duodenoduodenostomy complications are more

dangerous but endoscopic biopsy and hemostasis of duodenal ulcers of the transplanted pancreas-duodenum complex will be made feasible by this technique.

Systemic venous drainage is technically less demanding and used with less difficulty and more frequently by those surgeons who are familiar with kidney transplantation technique. In the early days of pancreas transplantation in the University of Minnesota, portal venous drainage was used for the pancreas graft venous effluent only in seven cases. Systemic hyperinsulinemia caused by systemic drainage first was showed by Diem et al (Diem et al, 1990). This concept lead Rosenlof et al (Rosenlof LK, et al, 1992) and Shokouh-Amiri et al (Shokouh-Amiri MH, et al, 1992) to recommend routine use of portal drainage for SPK transplants in 1992 because of its more physiologic pattern of insulinemia, although the carbohydrate metabolism is not different in both groups some authors showed that de-novo hyperinsulinemia predisposes to accelerated atherosclerosis (Fontbonne A, et al, 19991) and increasing the level of low density lipoprotein(LDL) (Hughes TA , et al, 1995) but its relevance to pancreas transplant recipients is not certain.

Some centers now use extra- or retroperitoneal approaches for better accessibility of the pancreas graft for postoperative routine percutaneous biopsies and easier arterial anastomosis and some of them suggest using an en bloc kidney-pancreas transplantation from the same donor. The technique of retroperitoneal pancreas transplantation with portal-enteric drainage was first described by Boggi et al in 2005 (Boggi et al, 2005). This method may be used in patient with severe intraperitoneal adhesions due to multiple previous abdominal surgeries and also for pancreas retransplant. Kahn et al described the same technique by systemic venous drainage (Kahn et al, 2008). They recommend this approach in obese patient with severe iliac artery atherosclerosis because of best exposure of the aorta and inferior vena cava by this method. In the en bloc techniques donor pancreas and left (or right kidney) is harvested en bloc in line with abdominal aorta so that the superior mesenteric, celiac artery and renal artery origins are maintained intact on the aorta and no arterial reconstruction by donor iliac artery would be needed in the back table procedure. Then the aorta could be used as the complex graft inflow conduit. Portal vein and renal vein may be anastomosed separately (Schenker P, et al, 2009) but we recommend to anastomose the graft portal vein to the left renal vein in the bench procedure, and then use the graft renal vein as the venous outflow of the graft. This will reduce the warm ischemia time by reducing the number of vascular dissections and anastomoses.

6. Immunosuppressive regimens

Unlike other solid organ transplantations, pancreas transplantation needs immunosupression for prevention of alloimmune rejection or autoimmune recurrence of diabetes mellitus even in transplant between identical twins (Sutherland DE, et al, 1984). In the early years of pancreas transplantation, only azathioprine and prednisone were used for immunosupression, but such a regimen was not adequate for prevention of rejection in PTA recipients (Sutherland et al, 2001). In the later years Minnesota antilymphocyte globulin added to this regimen for induction and maintenance immunosupression evolved to triple therapy by cyclosporine, azathioprine and prednisone. This change along with better surgical methods and better preservation of the deceased donor pancreas by UW solution resulted in better long term results of pancreas transplantation during the era of late 80's and early 90's. The pancreas rejection rate remained as high as 78% in this era (Stegall MD, et al, 1997). Gradually, cyclosporine and azathioprine were replaced by Tacrolimus

(Prograf™) and Mycophenolate mofetil (MMF, Cellcept™) during the later years and monoclonal anti T cell antibodies such as basiliximab and daclizumab added to induction immunosuppressive regimen of these patients. By use of these new regimens, risk of rejection decreased to less than 8-11% in the modern era of pancreas transplantation (Cantarovich D & Vistoli F, 2009).

The routine immunosupression regimen in most pancreas transplant centers includes a T cell depleting agent such as rabbit antithymocyte globulin (rATG or Thymoglobulin™) with a total dose of 4-12 mg/kg in divided doses, or alemtuzumab (Campath™) or an interleukin-2 receptor antagonist such as basiliximab (Simulect™) or daclizumab (Zenapax™) for induction immunosupression. We add a low dose intravenous methylprednisolone (Solumedrol™) in the day of operation to prevent allergic reactions to these agents. Unfortunately, these induction regimens only reduce the biopsy proven acute rejection (BPAR) episodes, but had no or modest effect on the patient or graft long term survival (Sutherland DE, 2009). Information about use of anti inter leukin-2 receptor antibodies are confounding. For example, Becker *et al.* found no significant differences in patient and graft survival comparing the outcomes of no induction versus daclizumab or basiliximab in 63 SPK transplant recipients receiving tacrolimus, MMF and prednisone. There was, however, a slightly higher rate of deaths due to sepsis in the anti-IL-2R induction group (Becker et al, 2006). Newer data mostly agree with the use of alemtuzumab for induction immunosuppression, without incurring a risk of increased infections or malignancies except for cytomegalovirus. (Sollinger et al, 2011) . A new randomized trial has showed that in the short term follow-up after SPK, alemtuzumab and rATG induction therapies has been similarly safe and effective but alemtuzumab is more cost-effective and has been associated with less BPAR episodes (Farney AC, et al, 2009).

For maintenance immunosupression, perhaps the best current regimen is prednisolone free or rapidly steroid tapering regimens which consist of tacrolimus and MMF combinations. Omitting the steroids from the maintenance regimens results in better wound healing and also prevents from steroid induced insulin resistance. Replacing the MMF with sirolimus has no effect on pancreas rejection rates, but had poorer long term kidney graft survival in the SPK recipients, because sirolimus accentuates the nephrotoxicity of tacrolimus (Gallon LG, et al, 2007). Tacrolimus per se had diabetogenic effects in other solid organ transplant recipients, but such an effect has not been shown in pancreas transplant recipients, may be due to more cautious use of this nephrotoxic drug in SPK recipients or use of healthier donors for pancreas transplantation (Ming CS & Chen ZH, 2007). Because of known nephrotoxicity of calcineurin inhibitors (CNIs) e.g. tacrolimus or cyclosporine, avoidance of these drugs in all pancreas transplant recipients who are potentially at risk of renal damage (SPK or PAK recipients) or future renal failure (PTA recipients) is desirable but all initial attempts with calcineurin inhibitor avoidance or minimization are less promising (Singh RP & Stratta RJ, 2008). Although newer agents such as sirolimus, everolimus, and CTLA-4 Ig are agents known to be either both nonnephrotoxic and nondiabetogenic or less so when compared with CNIs, but their impact on pancreas transplant results are not yet evaluated by randomized trials and their solitary use may be dangerous for the recipients and end up with graft loss (Cantarovich D & Vistoli F, 2009).

7. Postoperative care of pancreas transplant recipients

Perioperative care of pancreas transplant patients has no difference with any other major operation in diabetic patients. Kidney-pancreas recipients should be dilysed briefly for 1-2

hours before the operation to maintain the serum potassium below 5.5 meq/l and also to optimize the platelet function. Complete fluid removal is unnecessary. During the operation all of these patients need routine anesthesiologist monitoring with special attention to hemodynamic stability, tight control of blood sugar (to prevent both hypo- or hyperglycemia) and serum potassium, arterial blood gas and prevention of volume overload by keeping central venous pressure (CVP) around 8-10 mmHg. Ketoacidosis may be occur and should be prevented by intravenous insulin infusion if required. Sterile aseptic techniques are recommended for all venous and arterial line placements.

In kidney-pancreas recipients, usually kidney transplantation is done before the pancreas operation. During the kidney operation the patient is kept mildly volume expanded and before declamping the renal vasculature, the systolic blood pressure should be around 120 mmHg and Mannitol and furosemide should be infused as described in the other chapters of this book. Induction immunosuppressant (methylprednisolone or any types of t-cell receptor or interleukin-2 antibodies) usually started preoperatively and continued throughout the operation. Some surgeons advise to use these agents prior to declamping of vascular anastomoses.

After completion of kidney transplantation, the anesthesiologist should carefully monitor the brisk urine output and maintain it at least around 4 ml/kg/hour with appropriate fluid and electrolyte management throughout the remaining of the operation. Hypovolemia leads to acute tubular necrosis (ATN) of the renal allograft and volume overload will result in bowel and pancreas graft edema and may lead to postoperative abdominal compartment syndrome and graft dysfunction. Anticoagulation is not recommended for general kidney transplant alone recipients unless in the instance of presence of any other indications like mechanical heart valve or history of coagulopathy. But because pancreas is a low blood flow organ, especially when portal drainage is chosen as the preferred method for surgery, before clamping of the inflow veins or arteries, it's better to use systemic heparinization of the patient and we prefer to continue intravenous heparin postoperatively at least for 5 days to maintain the activated partial thromboplastin time (aPTT) around 1.5 times the normal value (between 55 – 85 seconds) to prevent graft vascular thrombosis.

After the operation the patient is transferred to transplant intensive care unit and CVP, vital signs, arterial blood gas, blood pressure, urine output and blood glucose are monitored continuously. Almost all patients are extubated in the operating room and don't need postoperative mechanical ventilation.

Kidney transplant patients usually have large urine outputs (as much as 20 liters/day) that should be replaced according to the patient fluid and electrolyte condition as discussed in the other chapters. Hypotension is usually due to intraabdominal bleeding (even in the absence of drainage from abdominal drains) or gastrointestinal bleeding from duodenal anastomosis and should be treated emergently by reexploration of the patient and fluid management. Hypertension should be avoided and treated appropriately to prevent bleeding and graft malfunction.

Oral immunosuppressive drugs (usually tacrolimus and MMF) are started after the day of operation. Prednisolone replaces intravenous methylprednisolone after 3 days by a dose of 0.5-1 mg/kg/day, but rapidly tapered to near zero during the next 4 weeks-3 months. All patients should receive prophylactic broad spectrum antibiotics for 2-5 days and most centers add antifungal drugs (such as amphotericin B or an azole derivative or caspofungin) and anti cytomegalovirus (CMV) drugs (e.g. gancyclovir) to this regimen. These protocols are different slightly among pancreas transplant centers and its better and mandatory that

each physician follow the routines of her/his center to avoid and confusion in the patients and personnel and future evaluations of the center. During the first 24 hours the patient may need small doses of intravenous insulin for maintaining the blood sugar below the 200 mg/dl because of delayed graft function or use of high doses of corticosteroids but after that or in case of any unusual increase in the serum glucose level, prompt assessment of graft vascular status by Duplex ultrasound and appropriate intervention should be done emergently. We routinely monitor the graft vasculature by Duplex ultrasound at least every 12 hours for 5 days after the operation. Many other means are available for continuous monitoring of graft function besides the blood sugar and duplex scanning. Serial measurements of serum amylase and/or lipase, C-peptide, and urine amylase and protocol ultrasonographic or computerized scan (CT) guided biopsies are among them (Han DJ & Sutherland DE, 2010).

Drains should be monitored for unusual leakage or bleeding and removed as soon as possible (usually after 5 days for pancreas drains and 24 after removing the Foley catheter for perirenal drain). Nasogastric tube remains until the return of gastrointestinal function usually for at least 72 hours. A recent study has showed that omission of a nasogastric tube has been associated with earlier return of bowel function, less discomfort, and shorter length of stay (Barth RN, 2008). Ambulation of the patient is desirable in the first 24 hours after the operation to prevent deep vein thrombosis and also other known complications of bedridden patients such as atelectasis or postoperative ileus.

8. Complications of pancreas transplantation

Despite large improvements in immunosuppression and surgical techniques, the history of pancreas transplantation, unlike that of other abdominal organ transplants, has largely been shaped by its associated complications (Troppmann C, 2010). We can discuss about these complications in 3 distinct categories: surgical, infectious, immunologic and other non-immunologic. Infectious complications are not specific for pancreas transplantation and many of their aspects are in common with other solid abdominal organ transplantation and discussion about them is presented in other chapters of this book.

Surgical complications

Surgical complications now decreased to at least 8% in large series reported by experienced pancreas transplant center s around the world and most of them frequently result in graft loss and increase recipient morbidity and mortality significantly and augment transplant cost considerably (Goodman J & Becker YT, 2009). Many of the surgical complications (such as hematuria, duodenocystostomy leakage, reflux pancreatitis, etc) are unique to the bladder drainage as previously discussed. These known complications lead pancreas transplant centers to avoid from bladder drainage and use this technique only for PTA cases. Over 25% of these cases require conversion of BD to ED.

Vascular thrombosis

Vascular thrombosis has remained the most common complication of pancreas transplant procedure with a frequency of 3-10% (Gruessner AC & Sutherland DE, 2009). Other major complications include: intraabdominal bleeding, gastrointestinal bleeding, leakage (from duodenal anastomosis), pancreatitis, pancreatic necrosis, pancreatic fistula, abscess formation and other complications of any other major abdominal surgery such as atelectasis,

pneumonia, deep vein thrombosis, wound infection, dehiscence, and cardiovascular problem which is common in diabetic and chronic renal failure patients.

Graft vascular thrombosis has many factors that most of them are technical because of several vascular anastomoses that needs for pancreas transplantation. Rotation during arterial reconstruction at the time of back table preparing, inadvertent intimal damage to the iliac artery Y-graft during harvesting and over inflation of the arteries during flushing are the known causes of arterial thrombosis. Higher donor age, cardiocerebrovascular cause of brain death and massive fluid resuscitation and hemodynamic instability of the donor and use of HTK as the preservation solution, especially when cold ischemia time is over 12 hours, and recipient hypercoagulable states or use of sirolimus are other important factors (Troppmann C, 2010). Venous thrombosis may be secondary to arterial thrombosis, severe pancreas rejection, and severe graft pancreatitis or may be completely technical or due to use of venous extension graft. There is no difference in the rate of graft thrombosis according to the venous drainage (systemic or portal) technique. Also PAK transplantation has been an independent risk factor for graft vascular thrombosis (Troppmann C, et al, 1996). Most centers use systemic heparinization for prevention of vascular thrombosis and continue this treatment for 5-7 days and after that change this regimen to 325 mg/day acetyl salicylic acid (ASA) or warfarin for selected cases (second transplants or confirmed hypercoagulable state), although some authors hadn't agree with this concept in the past (Sollinger HW, 1996). Usually the first sign of graft thrombosis is increasing the blood sugar level that should be promptly assessed by Duplex ultrasound. The patient may complain from abdominal pain and later abdominal tenderness will be revealed. Venous thrombosis will results in dark hematuric urine if bladder drainage had been used. Except for a few case reports most of these cases needs relaparotomy for graft removal, but if diagnosed early interventional radiologists or reanastomosis may be very rarely salvage the graft.

Leakage

Leakage from duodenojejunostomy or duodenoduodenostomy is a devastating complication of pancreas transplantation that may be associated with high morbidity and mortality, if recognized late. Because of spillage of enteric content, the patients develop signs and symptoms of peritonitis such as abdominal pain and tenderness, fever, high leukocytosis, and bilious content in abdominal drains. Sometimes this leakage is minor and the site of leakage contained by the greater omentum. Using broad spectrum antibiotics and Roux-en-Y reconstruction help more to obscuring the symptoms. In this situation, signs and symptoms may be obscure and only developing ileus, low grade fever, tachycardia and tachypnea, mild hyperglycemia, hyperamylasemia, low platelet count, will lead the surgeon to perform additional imaging studies (mostly abdominal CT scan) to diagnose this problem. The patient should be undergone exploration and in most cases the best option is graft pancreatectomy if peritonitis is diffuse or associated by multiple intraabdominal abscesses, or the patient ids unstable. Leakage from bladder drained pancreas may have milder symptoms and treated by combined bladder decompression and percutaneous drainage or conversion to enteric drainage. In cases of severe sepsis or diffuse infection, graft pancreatectomy is inevitable. Obscure leakages may be revealed as late as 2 weeks after the operation by abdominal abscess or pancreatic fistula that may be treated conservatively by percutaneous drainage, but many times the patient will prefer the graft to be removed because of the associated bothering complications such as skin excoriations by pancreas secretions. Also, pancreas fistula may be a complication of focal necrosis (due to

ischemia, rejection or infection) of the pancreas graft which communicate with the pancreatic duct or a complication of graft pancreatitis.

Many factors is contributed to anastomosis leakage, including technical errors, ischemia of the head of pancreas (due to vascular events, previous atherosclerosis of the donor, edematous duodenum at the time of reconstruction), reexploration for another causes, intraabdominal bleeding or diffuse primary peritonitis, severe acute rejections, and CMV infections. Some surgeons suggest that revascularization of the gastroduodenal artery or even the gastroepiploic artery may prevent ischemia of the head of pancreas and the duodenal C-loop (Nghiem DD, 2008 and Muthusamy ASR et al, 2008). We use this technique in every patient that the gastroduodenal artery is relatively large. This may also protect the duodenum from later ulcers and bleeding.

Pancreatitis

There is no uniformly accepted definition for graft pancreatitis, but all of the available definitions include the signs and symptoms of native pancreatitis with rising lipase and amylase, and maintained endocrine function (Troppmann C, 2010). Unfortunately these serum markers associated poorly with graft pancreatitis and may be prolong elevated after pancreas transplantation. Early pancreatitis is the result of poor graft handling, long ischemia time and preservation and reperfusion injury and may be visible during the operation, by graft edema and diffuse or focal fat necrosis around the graft. Prolonged cold ischemia time over 12 hours, use of HTK as the preservation solution and also poor donor quality are other risk factors (Han DJ & Sutherland DE, 2010). In case of bladder drained pancreas, pancreatitis may be the result of urine reflux. Most of these conditions are self limiting and adding the subcutaneous octreotide (0.1-0.2 mg every 8 hours) for 3-5 days after the operation, bowel rest and temporary total parenteral nutrition is the only treatment that needed. In rare cases it is so severe that the only option for treatment will be graft necrosectomy or pancreatectomy. In BD drained cases, the best treatment for resistant cases is conversion to enteric drainage. Rarely the cause of acute pancreatitis in these patients is CMV or other viral infections that if confirmed should be treated by gancyclovir or other antiviral agents.

Graft pancreatitis may be complicated just like the native pancreatitis with infections, pseudocysts, peripancreatic sterile fluid or pancreatic ascites, pancreatic fistula, and arterial or venous thrombosis or bleeding which should be treated accordingly.

Bleeding

Intraabdominal bleeding is relatively common after this operation. In most cases this is a technical error due to poor hemostasis of the pancreatic graft or the so many vascular anastomoses that used. Sometimes it is due to technical errors in the associated kidney transplant procedure. It may be due to heparin overdose that should be diagnosed by measurement of aPTT and if needs treated by protamine sulfate. Severe graft pancreatitis or pseudoaneurysms of the infected vascular anastomoses are another source of late abdominal bleedings in these patients that may be delayed as long as 2 weeks to several months after the operation. Early postoperative hypertension may cause transient bleeding from vascular anastomoses and through the abdominal drains that will be stopped spontaneously when the hypertension controlled appropriately with any need to reexploration.

Gastrointestinal bleeding is unique complication of enteric drainage. The site of bleeding may be duodenojejunostomy, distal jejunojejunostomy of the Roux-en-Y loop,

duodenoduodenostomy (DD) or mucosal ulcers in the graft duodenal C-loop (Nikeghbalian S, 2009) due to ischemia, rejection or CMV infection. One should rule out other sources of bleeding, such as native small bowel CMV infections, stress native gastric or duodenal ulcers by upper GI endoscopy or enteroscopy and also obscure site of bleeding such as neoplasm or angiodyplasia of the colon. If DD had been used for enteric drainage, endoscopy can be used for diagnosis and treatment. In other cases, angiography, red blood cell isotope scan, or enteroscopy may be used for diagnosis, but in most cases at last the best option is to explore the patient (Orsenigo E, et al, 2005).

Lymphocele and chylous ascites

Because of diverse perivascular dissections (around the aorta, IVC, superior mesenteric vein and iliac arteries and veins) in pancreas transplantation surgery, intraabdominal or perigraft sterile collections due to lymphorrehea are common. These collections may be so much that exit through the abdominal drains and when the patient returns on oral diet being frankly chylous. Perigraft collections are one of the causes of graft dysfunction and should be drains percutaneously. Chylous ascites is usually self-limiting and therapy is only supportive (replacing the fluid and electrolytes and use of oral short chain fatty acids and removing the drains to prevent lymphocyte and protein depletion. The best treatment is prevention by meticulous dissections and ligation of all perivascular lymphatics during the dissections.

Immunologic complications

Acute rejection

Rejection of the pancreas graft is as much as 40 % in the past and pancreas transplant recipients receive the highest level of immunosuppressant drugs among other abdominal organ transplantations. One-year rates of rejection have steadily decreased and are currently in the 10–20% range depending on case mix and immunosuppressive regimen (Singh RP &Strata RJ, 2008). The highest rate of graft loss due to immunologic rejection is seen in PTA recipients and the lowest incidence is in SPK patients, probably due to immunologic protective effect of the renal graft or earlier diagnosis of the rejections with better response to therapy. In the era that BD pancreas transplant was a routine the best indicators of pancreas transplant rejection was decreasing urine amylase and lipase which was preceded by hyperglycemia. In other words, BD experience showed that pancreas exocrine function is affected sooner that its endocrine function and when hyperglycemia presents it would be too late to salvage the pancreas from acute rejection. In the SPK patient, increasing the serum creatinine due to rejection usually preceded the hyperglycemia, and then diagnosis of the renal graft rejection actually means the pancreas rejection as well and both can treated simultaneously by the same antirejection treatment except for rare instances. Nowadays, with increasing experience, protocol percutaneous pancreas biopsies are routine procedure in the armamentarium of any major pancreas transplant unit. By these timely scheduled biopsies, every pancreas rejection could be diagnosed before its clinical and paraclinical symptoms present but until now the controversies continued about the candidates and interval of this time of protocol biopsies for the surveillance of pancreas graft rejection (Gaber LW, 2007).

It's shown that HLA mismatch is a major contributor to pancreas rejection and fully HLA matched recipients has the lowest levels of rejections when on the same immunosuppressive protocol (Burke, et al, 2004). Other series showed that combination immunosuppressive therapy including T-cell depleting antibodies for induction, tacrolimus and MMF could improve the outcome significantly, even in poorly HLA matched PTA recipients (Gruber

SA, et al, 2000). However, in the PTA and PAK categories, HLA matching has remained an important outcome factor (Han DJ & Sutherland DE, 2010).

Signs and symptoms of pancreas rejection are obscure. Only 5-20% of patients developed mild fever, abdominal pain or distension or sometimes ileus or diarrhea (Sutherland DE, et al, 2010). The clinicians should be rely on paraclinical markers and after performing the biopsy the best approach is to treat empirically when a combination of paraclinical changes support existence of an acute rejection episode, if the results of the biopsy prepare with delay. The best treatment for confirmed acute rejection episodes is the use of pulse methylprednisolone therapy plus increasing the dose of oral drugs or adding the sirolimus to the previous drugs. Nephrotoxicity and diabetogenic effect of tacrolimus, and effect of corticosteroids on insulin resistance induction should be in mind. In severe cases use of thymoglobulin or other T-cell depleting antibodies may be required. As previously described many immunosuppressive protocol are under investigation now to better prevent these acute rejection episodes which most of them focused on corticosteroid spring and also use of T-cell depleting antibodies for induction.

Chronic rejection

Previously, chronic rejection does not appear to be as large a problem for pancreas-transplant recipients as it does for renal-transplant recipients (Hopt UT & Drognitz O, 2000). As the number of pancreas transplants surviving beyond the first year increases, chronic rejection is becoming increasingly common (Burke, et al, 2004). The rate of pancreas loss to chronic rejection was 8.8% in 914 pancreas transplants followed for 3 years. Chronic rejection was highest in the PAK (11.6%) and PTA (11.3%) and lowest for SPK (3.7%)(Humar A ,et al, 2003). The most important pathologic changes in chronic rejection are replacing the pancreas tissue with fibrous band with distortion of architecture and loss of acini (Gaber LW, 2007). The severity of chronic rejection is not correlated well to the graft loss, but clinically the patients become hyperglycemic, first with response to oral hypoglycemic agents and then low dose insulin injection an at last completely depend on insulin injection for the rest of their lives. There's no definite treatment for this type of rejection, which may be simply a non-immunologic "physiologic wear and tear "of the organ, but some authors try to use sirolimus in these conditions (Matias P, et al 2008).

Non-immunologic complications

One the known complications of every solid organ transplant is primary nonfunction or delayed graft function. Primary non-function is a definition of inclusion. No other cause of graft nonfunction should be found, e.g. graft vascular thrombosis, graft necrosis, or severe acute rejections or pancreatitis. In this condition the graft is viable and non-inflamed with no need for pancreatectomy, but no insulin secretion is found and the patient needs insulin injection as his/she preoperative situation. Some patients transiently need low doses of insulin for their blood glucose hemostasis, but after a maximum of 1 week this requirement decreased to zero. This condition is named "delayed graft function". In both of this condition no frank anatomic or pathologic changes in the graft is found in the postoperative assessment of the patient. Poor donor quality and poor handling of the graft is the only causes that may contribute to these conditions.

Other non surgical and non-immunologic complications also may be seen in these diabetic patients. Many of these are due to preoperative diabetic complications. Delayed gastric emptying (gastroparesis), constipation or diarrhea, dizziness and lightheadedness (all due to autonomic neuropathy), peripheral neuropathy, poor visual acuity (accelerated

retinopathy)and accelerated cataract are among these complications. Many of these diabetic signs and symptoms are multifactorial and side effects of the immunosuppressant drugs and multiple other antifungals and antivirals that used for these patients plus preoperative poor diabetic control accelerates them. Every effort should be used to diagnose the treatable causes and treat them accordingly. For example for diabetic gastroparesis, use of erythromycin or domeperidone has been moderately successful (Zaman f, et al, 2004). Intractable diarrhea may be due to CMV or other microbial or protozoal infections which should be treated. But when no known cause is found, the best treatment is dividing the dose o MMF to 4 times a day and also use of subcutaneous octreotide. Also every transplant team member should be completely remember the common complications of the immunosuppressive drugs and treat them appropriately or change the drugs if possible.

9. Long term results of pancreas transplantation

Long term results of pancreas transplantation improve day by day with better surgical experience and use of more potent immunosuppressive regimen. Pancreas graft 1 year survival rate improves from 75% in 1998 to 85% at the end of 2003 for SPK cases, and from 55 to 77% for PAK and from 45 to 77% in PTA patients (Gruessner AC & Sutherland DE, 2005). This improvement also is seen in PTA patients that traditionally have the worst outcome, as shows in many studies. For example in a report Stratta et al. by 1 year patient and graft survival has increased to 96% and 86%, respectively (Stratta RJ, et al, 2003). In one the largest recently published studies, the 5-year, 10-year, and 20-year patient survival for SPK recipients was 89, 80, and 58%, respectively (Wai PY & Sollinger HW, 2011).

Now, by decreasing the technical failures, the randomized studies to valuate other effective factors can be performed with better accuracy and less confounding bias. Perhaps the best statistics that show the effect of pancreas transplantation is the statistics about comparing the patient survival in kidney transplant alone recipients with SPK patients. Even in older studies, life expectancy of younger recipients (less than 50 years) of SPK is 10 years longer than diabetic patients who only received a kidney graft from deceased donors (23.4 years *vs* 12.9 years) (Tyden G, et al, 1999, Ojo AO,etal, 2001). When both grafts were procured from deceased donors, SPK transplant recipients has better survival rate than kidney transplant alone (KTA) recipients but this difference is not significant when KTA patients received their grafts from living donors. The presence of a functioning pancreas graft improved survival by 20% at 8 years (Reddy KS, 2003).

Patient survival is not statistically different according to the type of exocrine drainage (BD vs. ED), but quality of life is better and overall complications is less when BD is used (Sollinger HW, et al, 2009). Despite the improved survival, the most common type of death in these patients is death with a functioning graft and cardiovascular morbidity remains a major contributor to patient outcome in these patients (Sollinger HW, et al, 2009).

Comparing with KTA recipients, quality of life in those 95% of patient who survive after SPK transplantation is improved significantly, due to cessation of insulin injections, multiple needling for glucose monitoring and better emotional status (Sutherland De, et al, 2001 & Joseph JT, et al, 2003).

Effect on end organ damage

Pancreas transplantation improves glycemic control in long term follow up, manifested by lower hemoglobin A_{1C} level, improved lipid profile and insulin mediated protein kinetics,

normal hepatic glucose production and counter-regulatory effects of glucagon to hypoglycemia (White SA, et al, 2009).

Sollinger et al suggests that despite numerous reports of improvement in secondary diabetic complications after SPK, retinopathy and cardiac or vascular complications of diabetes are not reversible and show no improvements after SPK, but severe (peripheral and autonomic) neuropathy is an exception to this rule (Sollinger et al, 2009). Diabetic retinopathy will deteriorate after pancreas transplantation in over 30% of patients if it is in an advanced proliferative phase prior to the operation, but after 3 years the pancreas transplantation results in stabilization of retinopathy progression (Chow VC, et al, 1999). Cataract is a known complication of any organ transplantation and is the results of corticosteroids and calcineurin inhibitors and may become evident after pancreas transplantation as well.

Macrovascular effects of diabetes may not improve after pancreas transplantation, especially because of calcineurin inhibitor (CNI) effect on weight gain, dyslipidemia and hypertension, and many other risk factors that are very common in diabetic patients. Also the peripheral vascular disease in diabetics is often far too advanced to reverse. Because, most centers exclude patient with Macrovascular diabetes complications and no conclusive study exists about effect of pancreas transplantation on natural history of macrovascular disease in these patients (Sutherland De, et al, 2001). Deterioration depends on the ongoing risks. Some centers show the benefits of pancreas transplantation on cerebrovascular system, but again the results are inconclusive. Coronary artery disease, diastolic function, left ventricular geometry and cardiac autonomic function may be improved after SPK comparing with KTA recipients after a few years (White SA et al, 2009).

Normoglycemia also improves the diabetic glumerulopathy (but does not reverse it) and decrease the proteinuria. On the other hand, use of CNIs per results in nephropathy and may decrease the creatinine clearance. SPK recipients may not survive enough to benefit from the effects of normoglycemia on their nephropathy. In diabetic KTA recipients, the diabetic nephropathy is progressively leading to lower kidney graft survival and many studies show that PAK transplantation may improves the kidney graft survival by prevention of accelerated diabetic glumerulopathy in these patients.). Some studies shows that PTA (if done early enough) can preserve renal function, but It takes at least 5 years until a pancreas transplant can reverse the lesions of diabetic nephropathy (Sutherland De, et al, 2001).

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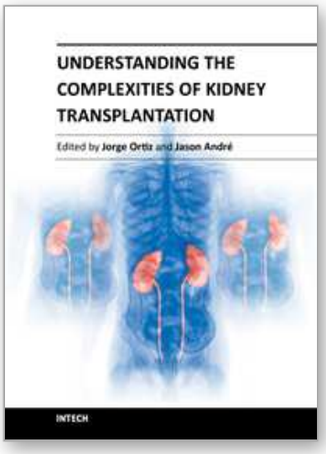

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Kidney transplantation is a complex field that incorporates several different specialties to manage the transplant patient. This book was created because of the importance of kidney transplantation. This volume focuses on the complexities of the transplant patient. In particular, there is a focus on the comorbidities and special considerations for a transplant patient and how they affect kidney transplant outcomes. Contributors to this book are from all over the world and are experts in their individual fields. They were all individually approached to add a chapter to this book and with their efforts this book was formed. Understanding the Complexities of Kidney Transplantation gives the reader an excellent foundation to build upon to truly understand kidney transplantation.

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