In Brief

Pancreas transplantation is considered the best treatment option for patients with type 1 diabetes and renal failure. In this article, the authors describe peri-operative glucose control in patients undergoing pancreas or kidney-pancreas transplantation.

Glucose Control During and After Pancreatic Transplantation

M. Hosein Shokouh-Amiri, MD; Robert J. Stratta, MD; Kashif A. Latif, MD; and Osama Gaber, MD

After decades of controversy surrounding the therapeutic validity of pancreas transplantation (PTX), the procedure has become accepted as the preferred treatment for patients with insulin-requiring diabetes mellitus and advanced diabetic nephropathy. The trade-offs for normal glucose homeostasis are the operative risks of the transplant procedure and the need for chronic immunosuppression. Free islet grafts have the same potential but do not approach PTX in terms of consistency of results.

From December 1966 to October 2000, more than 15,000 PTX procedures were performed worldwide and reported to the International Pancreas Transplant Registry (IPTR).[1] In the past decade, the majority (82%) of PTX procedures have been performed in combination with a kidney transplant (simultaneous kidney-pancreas transplant [SKPT]) in patients with end-stage diabetic nephropathy. The current 1-year actuarial patient and kidney and pancreas (with complete insulin independence) graft survival rates after SKPT are 95, 92, and 84%, respectively.[1,2] Solitary PTX procedures comprise the remaining activity, including either sequential pancreas-after-kidney transplants (PAKT, 12%) or transplant of pancreas alone (PA, 6%). The current 1-year patient survival rate after solitary PTX is 95%, and the 1-year actuarial pancreas graft survival rates are 72% for PAKT and 71% for PA.[1,2]

The Diabetes Control and Complications Trial (DCCT) has clearly shown that improved glycemic control lowers the risk of secondary diabetic complications.[3] However, intensive insulin therapy did not result in normalization of hemoglobin A_{1c} (HbA_{1c}) levels, was associated with a threefold increased risk of severe hypoglycemia, and was resource-intensive. The results of the DCCT provide a strong rationale for pancreas transplantation.

Recipient Selection

Patient selection is aided by a comprehensive medical evaluation before transplantation (Tables 1 and 2) performed by a multidisciplinary team that confirms the diagnosis of diabetes, determines the patient's ability to withstand the operative procedure, establishes the absence of any exclusion criteria (Table 3), and documents end-organ complications for future tracking after transplantation.[4] The primary determinants for recipient selection are the presence of diabetic complications, degree of nephropathy, and cardiovascular risk (Table 1).

With increasing experience, previous absolute contraindications have become relative contraindications, and relative contraindications have become risk factors for PTX (Table 3). Binocular blindness or history of a

Table 1. Indications for Pancreas Transplantation: Eligibility Guidelines

I. Medical Necessity

- A. Presence of insulin-treated diabetes mellitus:
  1. Documentation of insulin dose
  2. Type 1 or type 2 diabetes
- B. Ability to withstand surgery and immunosuppression (as assessed by pretransplant medical evaluation):
  1. Adequate cardiopulmonary function
     - a. Cardiac stress testing ± coronary angiography to rule out significant coronary artery disease or other cardiac contraindications
     - b. Patients with significant coronary artery disease should have it corrected before transplant
  2. Absence of other organ system failure (other than kidney)
- C. Emotional and sociopsychological suitability
- D. Presence of well-defined diabetic complications (any two of the following):
  1. Proliferative retinopathy
  2. Nephropathy (hypertension, proteinuria, or decline in glomerular filtration rate)
  3. Symptomatic peripheral or autonomic neuropathy
  4. Microangiopathy
  5. Accelerated atherosclerosis (macroangiopathy)
  6. Glucose hyperlability, insulin resistance, or hypoglycemia unawareness with a significant impairment in quality of life
- E. Absence of any contraindications
- F. Financial resources

II. Type of pancreas transplant

- A. Specific entry criteria based on degree of nephropathy:
  1. Simultaneous kidney-pancreas transplant: creatinine clearance <30 ml/min
  2. Sequential pancreas after kidney transplant: creatinine clearance ≥40 ml/min (on calcineurin inhibitor); >55 ml/min if not on calcineurin inhibitor
  3. Pancreas transplant alone: creatinine clearance >60–70 ml/min and 24-h protein excretion <2 g
- B. Primary determinants for recipient selection are the presence of diabetic complications, degree of nephropathy, and cardiovascular risk

major amputation are not necessarily contraindications for PTX, provided that the patient is well adjusted to these otherwise irreversible diabetic complications. Inclusion and exclusion criteria for PTX are listed in Tables 1 and 3.

The cardiac status of each candidate must be assessed carefully because significant (and silent) coronary artery disease is not uncommon in this population. The cardiac evaluation consists of a noninvasive functional assessment, such as an exercise or a pharmacological stress test, in addition to echocardiography. Coronary angiography is reserved for specific indications such as age >45 years, diabetes for >25 years, a positive smoking history, long-standing hypertension, previous major amputation due to peripheral vascular disease, history of cerebrovascular disease, or cases in which the history, physical examination, or noninvasive cardiac studies reveal an abnormality.[4]

A history of previous myocardial infarction (MI), angioplasty, stenting, or coronary artery bypass grafting are not contraindications for PTX, as excellent outcomes have been reported in patients with previous cardiac interventions.[5] However, sudden cardiac death, in the absence of significant structural heart disease, continues to be a major cause of cardiac mortality after PTX.[6] For this reason, a number of centers are beginning to test cardiac autonomic function in these patients, using laboratory-evoked cardiovascular tests and 24-h heart-rate variability measurements.[7] The new methodology may be able to detect alterations in autonomic function before the onset of disabling symptoms.

In general, age >65 years, heavy smoking, a left ventricular ejection fraction <30%, recent MI, and severe obesity (>150% ideal body weight or body mass index [BMI] >30 kg/m^2) are usually viewed as contraindications for PTX (Table 3).[4] Most patients <45 years of age are acceptable candidates for PTX provided that no significant coronary artery disease is present. Diabetic patients >45 years of age are not candidates until proven otherwise and need to undergo an extensive cardiovascular and peripheral vascular evaluation. Potential male recipients >100 kg and female recipients >80 kg, depending on their height and body habitus, have a higher rate of surgical complications after PTX. For this reason, a BMI >30 kg/m^2 is considered an absolute contraindication and BMI >27.5 kg/m^2 is a relative contraindication for solitary PTX.

Preoperative Preparations for Pancreas Transplantation

Patients are allowed nothing by mouth once an organ becomes available. Patients' blood glucose is checked every 2 h, and insulin is supplemented as needed to keep the blood glucose between 100 and 150 mg/dl. If blood glucose is labile, then an insulin infusion is started. This consists of a mixture of 250 units of regular insulin in 250 cc of 50% saline, with a final concentration of 1 unit of insulin/ml of infusion fluid. The initial basal rate is 0.2–0.3 unit/kg/h, which is then titrated with blood glucose determinations every 1–2 h to maintain the blood glucose in the range noted above according to the scale shown in Table 4.

Intraoperative Monitoring

Essentially the same regimen of infusion is followed intraoperatively as the preoperative infusion, with the strict rule to maintain euglycemia. Following a successful pancreas transplantation,[8] the transplanted pancreas will take over glycemic control.

Postoperative Management

Insulin therapy, as outlined in Table 4, can take one of two forms. The first involves instituting aggressive insulin therapy with the objective of "complete" insulin replacement to "rest" the β-cells in the transplanted pancreas for the first few days following surgery. The second is to let the transplanted pancreas function as soon as blood supply is restored to the transplanted organ. Each of these approaches has its proponents. The advantages of each are discussed below.

Complete replacement

Some practitioners believe that providing complete replacement of insulin will "rest" the β-cells in the transplanted pancreas and therefore preserve their function and avoid injury from acute stress. After 3–4

Table 2. Evaluation of Pancreas Transplant Candidates

1. Interviews and Consults
   - A. History and physical examination by nephrologist, endocrinologist, and transplant surgeon
   - B. Ophthalmology evaluation, including visual acuity, fluorescein angiography, retinal fundus photography with retinopathy score, and slit-lamp examination
   - C. Transplant coordinator and medical social worker interview, including completion of quality-of-life questionnaire
   - D. Gynecology consultation for all females (pelvic examination with Pap smear)
   - E. Dental evaluation
   - F. When indicated, additional evaluations may be required by orthopedic surgery, podiatry, psychology, psychiatry, neurology, or gastroenterology.
2. Cardiovascular, Respiratory, and Peripheral Vascular Evaluations
   - A. Standard testing includes orthostatic vital signs, 12-lead electrocardiogram, chest radiograph, echocardiography, and exercise treadmill, stress thallium, or dobutamine stress echocardiography.
   - B. Additional studies may include arterial blood gases, 24-h Holter monitoring, autonomic and peripheral vasomotor reflexes, Doppler arterial studies, ankle/brachial index, transcutaneous oxygen monitoring, plethysmography, carotid Doppler examination, aortography with run-off, or pulmonary function tests as indicated.
   - C. Cardiology consultation with or without coronary angiography as indicated
3. Metabolic and Endocrine Evaluation
   - A. Standard testing includes fasting blood glucose, HbA_{1c}, and fasting lipid panel (cholesterol, triglycerides, and HDL cholesterol).
   - B. Fasting and stimulated C-peptide levels are used to assess type of diabetes, if needed
   - C. Additional studies may include oral or intravenous glucose challenge, anti-insulin and islet cell antibodies, proinsulin level, and lipoprotein profile.
4. Genitourinary/Renal Evaluation
   - A. Standard testing includes electrolytes, blood urea nitrogen, serum creatinine, urinalysis with culture, and 24-h urine for protein and creatinine clearance.
   - B. Voiding cystourethrogram and urodynamics when indicated
   - C. Radiometric glomerular filtration rate if needed
   - D. In addition, kidney biopsy may be indicated.
   - E. Calcineurin inhibitor challenge test when indicated
   - F. Hormonal profiles as indicated
   - G. Evaluation of erectile dysfunction when indicated
5. Serology and Immunology Evaluation
   - A. ABO blood type and HLA tissue type
   - B. Cytotoxic antibodies
   - C. Viral titers (Epstein Barr virus, Herpes Simplex virus, Varicella-Zoster virus, Human Immunodeficiency virus, Hepatitis B virus, Hepatitis C virus, and Cytomegalovirus); polymerase chain reaction quantitation when indicated
   - D. Venereal Disease Research Laboratory/fluorescent treponemal antibody test for syphilis
6. Other Laboratory Tests
   - A. Complete blood count with differential and platelets, prothrombin time, partial thromboplastin time, chemistry profile, amylase, lipase
   - B. Abdominal ultrasound of kidneys and gallbladder
   - C. Mammography in females >35 years of age
   - D. Hemoccult × 3; contrast studies or endoscopy when indicated
   - E. Nerve conduction studies, gastric emptying scan, electromyography (when indicated)
   - F. Hypercoagulable work-up (when indicated)

days of total insulin replacement, patients are switched to an intermittent regimen that only delivers insulin to maintain euglycemia, and the β-cells take over the primary function of producing insulin.

The main disadvantage of this method is the inaccuracy that comes when precise protocols are not used to replace basal and bolus insulin. If doses are adjusted without allowing for the stress of surgery and insulin resistance that may develop from the use of immunosuppressants such as steroids and FK506, erratic blood glucose levels may result. Another disadvantage of this protocol is that the precise status of the function and viability of the transplanted organ is difficult to judge when insulin production is suppressed due to exogenous replacement. This could prevent assessment of compromised pancreatic function.

Replacement of insulin as needed

The authors, with years of experience in the field of pancreas transplantation, use a simple approach that allows the β-cells to autoregulate their secretion in response to blood glucose. Our studies (by the use of C-peptide) indicate that such patients can produce enough insulin in the graft as soon as the blood supply is restored to the pancreas after the transplant.

We prefer this approach when the islets are producing the insulin for the host. The blood glucose is checked every 2 h, and exogenous insulin, if needed, is given every 2 h to maintain euglycemia. A sudden increase in insulin requirement is a red flag that the function of the graft is affected. In this case, immediate intervention needs to be undertaken to protect the grafted organ (see below).

A need for supplemental insulin in the early postoperative period can be expected because of the immunosuppressive medications, which can also cause insulin resistance. Once the dose of steroids is tapered, the need for additional coverage declines.

Postoperative hyperglycemia also responds very well to the newer classes of oral antidiabetic medications, such as the insulin sensitizers, as long as strict guidelines for the use of such medicines are followed. If the need for supplemental insulin is caused by inadequate production of insulin by the graft (determined by C-peptide assay) or because of its small size for the host, then oral agents, such as sulfonylureas, may be beneficial.

Assessment of the Transplanted Organ

It is expected that from the time of pancreas allograft reperfusion, patients should become insulin-independent. Any abnormality of glycemic control should be investigated immediately, because some of the causes need immediate intervention in order to prevent graft loss. The usual causes of graft dysfunction are:

1. inadequate islet cell mass transplanted;

Table 3. Absolute and Relative Contraindications and Risk Factors for Pancreas Transplantation

I. Absolute Contraindications
- A. Insufficient cardiovascular reserve (one or more of the following):
  1. Coronary angiographic evidence of significant non-correctable or untreatable coronary artery disease
  2. Recent myocardial infarction
  3. Ejection fraction <30%
- B. Active infection
- C. History of malignancy diagnosed within past 3 years (excluding non-melanoma skin cancer)
- D. Positive human immunodeficiency virus serology
- E. Positive Hepatitis B surface antigen serology
- F. Active, untreated peptic ulcer disease
- G. Ongoing substance abuse (drug or alcohol)
- H. Major ongoing psychiatric illness
- I. Recent history of noncompliance
- J. Inability to provide informed consent
- K. Any systemic illness that would severely limit life expectancy or compromise recovery
- L. Significant, irreversible hepatic or pulmonary dysfunction
- M. Positive crossmatch

II. Relative Contraindications
- A. Age <18 or >65 years
- B. Recent retinal hemorrhage
- C. Symptomatic cerebrovascular or peripheral vascular disease
- D. Absence of appropriate social support network
- E. Extreme obesity (>150% ideal body weight or BMI >30 kg/m^2)
- F. Active smoking
- G. Severe aorto-iliac vascular disease

III. Risk Factors
- A. History of myocardial infarction, congestive heart failure, previous open heart surgery, or cardiac intervention
- B. History of major amputation or peripheral bypass graft
- C. History of cerebrovascular event or carotid endarterectomy
- D. History of hypercoagulable syndrome

2. high doses of corticosteroid and FK506 in the peritransplant period;
3. allograft pancreatitis; or
4. technical problems with blood supply to the pancreas allograft.

Pancreas allograft function is monitored meticulously by both serum and drain fluid amylase, lipase, and frequent blood glucose measurement, and the need for exogenous insulin requirement. Any allograft dysfunction will warrant the following work-up:

1. Serum C-peptide measurement to assess β-cell function. However, this assay is not immediately available at all facilities.
2. A Doppler ultrasonography of the allograft to verify the presence of flow to and from the allograft and the presence of fluid collection around the pancreas or swelling of the gland.
3. If the gland is difficult to visualize because of gas overlying the graft, a CT with contrast to demonstrate the viability of the allograft and/or the presence of pancreatitis. Radionucleotide study is of limited use.
4. An angiogram to demonstrate any blood flow problem to the allograft.

Patients are discharged 7–10 days after surgery, usually with no need for supplemental insulin. Thereafter, they are followed up by a team of specialists, including the transplant team, endocrinologist, clinical psychologist, and physiatrist. We believe the chance for best outcomes is enhanced with a team approach. However, one physician, usually the surgeon, has to be in charge.

Discussion

Most PTX recipients find the transition to transplantation easier than continued insulin therapy. There is now compelling evidence that PTX is not only acutely life-enhancing, but also chronically life-saving.[9] It is hoped that the beneficial changes in carbohydrate and lipid metabolism that occur early after PTX will translate into long-term improvements in diabetic end-organ complications and decrease the risk of atherosclerotic vascular disease.

In addition to correcting dysmetabolism and freeing patients from exogenous insulin therapy, data are emerging on the effects of PTX on the course of secondary complications.[9,10] With regard to nephropathy,[11] preliminary evidence suggests that successful PA transplantation can induce regression of early, but not advanced, microscopic lesions of diabetic nephropathy and stabilize renal function, whereas successful PAKT can prevent the recurrence of diabetic nephropathy in a kidney transplant.

The progression of diabetic retinopathy appears to be less favorably influenced by a functioning PTX. However, with longer follow-up (more than 4 years), data are accumulating to suggest that retinopathy may be stabilized.

Peripheral and autonomic neuropathies improve or stabilize in most PTX recipients, which may actually translate into a survival advantage. Improvements in nerve conduction velocity, gastric function, cardiac function, and a beneficial effect on microcirculatory blood flow have been demonstrated.[10] These effects may place patients at a lower overall risk for the development of peripheral ulcers or amputations.

There is also evidence that a functioning PTX may ablate the hyperlipidemic effects of immunosuppression and actually improve lipid metabolism over time. However, long-term studies are needed to fully document and characterize the effects of successful PTX on the diabetic condition.

Table 4. Blood Glucose Control by Frequent Measurements and Corresponding Insulin Requirements

Blood Glucose (mg/dl)	Infusion Rate
<50	Suspend drip
50–75	Reduce by 50%
75–100	Reduce by 25%
100–150	No change
150–175	Increase rate 2cc/h
175–200	Increase rate 4cc/h
200–225	Increase rate 6cc/h
225–250	Increase rate 8cc/h Check ketones

Solitary PTX has assumed an increasingly important role in the treatment of diabetes and currently accounts for more than 20% of PTX activity in the United States. In the future, advances in immunosuppressive strategies and diagnostic technology will only enhance the already good results achieved with solitary PTX. Further documentation of the long-term benefits and effects of PTX may lead to wider availability and acceptance, particularly from a reimbursement standpoint.

Effective control of rejection, with earlier diagnosis or better prevention, may soon permit solitary PTX to become an accepted treatment option in diabetic patients without advanced complications. Such a policy, if applied correctly, might actually reduce the number of diabetic patients requiring kidney transplantation in the future.

Other strategies for the treatment of diabetes are being actively investigated, including islet cell and fetal pancreas transplants, gene therapy, implantable insulin pumps, and bio-hybrid artificial pancreas units. Although any or all of these complementary methods may have a role in the treatment of diabetes in the future, it will be difficult for these alternative strategies to improve on the metabolic efficiency of the vascularized PTX that is achieved at present.

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M. Hosein Shokouh-Amiri, MD; Robert J. Stratta, MD; and Osama Gaber, MD, are professors of surgery in the Department of Surgery (Division of Transplantation), and Kashif A. Latif, MD, is a fellow in endocrinology and metabolism in the Department of Medicine at the University of Tennessee, in Memphis.