Pancreas-kidney transplantation in diabetes mellitus: Patient selection and pretransplant evaluation

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- Pancreas and kidney transplantation is a therapeutic option for patients with insulin-requiring diabetes and advanced chronic kidney disease (CKD) or end-stage kidney disease (ESKD).

- The majority of these patients receive a simultaneous pancreas-kidney (SPK) transplant, although some will receive a sequential pancreas after kidney (PAK) transplant.

- Patients with insulin requiring diabetes with normal or near-normal kidney function may be considered for pancreas transplant alone (PTA) if they have:

- Hypoglycemic unawareness
- Brittle diabetes with wild variations in blood glucose levels
- And/or if their quality of life is unacceptable because of diabetes-related sequelae.

- In general, SPK and PAK transplants are primarily indicated for patients with type 1 diabetes.

- However, SPK and PAK transplants may be performed for some patients with insulin-requiring diabetes who meet certain selection criteria and exhibit a type 2 diabetes phenotype.

- Type 2 diabetes phenotype may be characterized by :
  - The presence of detectable C-peptide levels
  - Older age of onset of diabetes (and older age at transplant)
  - History of non-insulin requiring diabetes preceding the need for insulin therapy
  - Shorter duration of insulin dependence
  - History of obesity
  - Non-caucasian race
- Whether these patients truly have type 2 diabetes is subject to debate, but clearly they do not meet the classic presentation of type 1 diabetes.

- In addition to exhibiting the above phenotypic characteristics, potential SPK and PAK transplant candidates with non-type 1 diabetes usually meet the following selection criteria:

- Age <60 years
- Body mass index (BMI) <30 kg/m2
- Insulin requiring for a minimum of three years with a total daily insulin requirement <1 unit/kg/day
- Fasting C-peptide level <10 ng/mL
- Presence of complicated or hyperlabile diabete

- It is important to note that data on how either C-peptide levels or total daily insulin requirements relate to outcomes following pancreas transplantation are sparse and incompletely understood.
- The above guidelines are based upon the assumption that patients with extreme insulin resistance may not be appropriate candidates for pancreas transplantation.
- Selection criteria for SPK and PAK transplant are variable and center specific as some centers will exclude any patient with detectable C-peptide levels.
- International Pancreas Transplant Registry (IPTR) data as well as a number of single-center reports suggest that measuring C-peptide levels is largely irrelevant in terms of either patient selection or predicting outcomes.

- Moreover, individual centers may have other cut-offs for SPK or PAK candidate exclusion, such as age above 50 years or BMI >28 kg/m2.
- Alternatively, other centers may transplant patients up to 65 years of age and with a BMI of 30 to 35 kg/m2

- Patients qualifying for an SPK or PAK transplant are usually referred to the transplant center by a nephrologist because of stage 4/5 CKD.
- Approximately 16 percent of SPK transplants are performed in patients prior to the initiation of dialysis therapy .
- Most of these patients will have advanced diabetic nephropathy, but some may have kidney disease from a condition other than diabetes.
- Thus, ESKD does not have to be secondary to advanced diabetic nephropathy to qualify for either SPK or PAK transplantation if the patient has insulin-requiring diabetes.
- This unique situation offers the opportunity to treat both the kidney disease and insulin-requiring diabetes successfully regardless of cause

Selection of optimal procedure

- The selection of the optimal procedure for individual patients depends upon patient-specific factors and organ availability.

- For younger patients (ie,<45 years old) with type 1 diabetes who have no other cardiac risk factors and few other comorbidities, in the absence of a living-kidney donor,simultaneous pancreas-kidney (SPK) transplant provides the best survival compared with either dialysis or deceased-donor kidney transplantation alone(KTA).

- However, because the one- and four-year mortality for waitlisted SPK transplant candidates has been reported to be 6.6 and 41.3 percent, respectively , performing a living-donor KTA may be preferred if an individual is facing:
- A long waiting time for SPK transplantation
- Is not doing well on dialysis
- Or has "stable" diabetes

- Not all patients with insulin requiring diabetes and ESKD qualify for SPK transplant or are even interested in receiving a pancreas transplant, particularly if :

- They believe that their diabetes is well controlled
- Not experiencing extreme glucose hyper-lability, hypoglycemia unawareness
- Not experiencing life-threatening, sight threatening, limb-threatening, progressive, or accelerated complications of diabetes

- In general, if a patient believes that diabetes is controlling their life more than they are controlling their diabetes, or if the presence of diabetes causing a significant impairment in their overall quality of life, then either SPK or PAK transplantation should be considered as a treatment option.

Patient selection

- The primary determinants for recipient selection are the presence of:

- Glucose hyperlability reflecting underlying insulin deficiency
- The degree of difficulty in achieving adequate glucose control
- Progressive diabetic complications (including CKD)
- Cardiovascular risk and iliac vascular disease
- Other comorbidities (eg, substance abuse, lung or liver disease, obesity)
- Emotional and psychosocial stability
- Overall functional and performance status

Age

- Appropriate candidates for simultaneous pancreas-kidney (SPK) transplantation are generally younger than kidney transplantation alone (KTA) candidates with diabetes, reflecting several factors:

- Patients with type 1 diabetes mellitus tend to develop end-stage kidney disease (ESKD) at an earlier age than patients with type 2 diabetes mellitus.
- Longstanding diabetes contributes to a higher incidence of other complications, such as cardiovascular disease, which affects transplant candidacy.

- An analysis of the United Network for Organ Sharing (UNOS) database including 20,854 pancreas transplant recipients between 1996 and 2012 demonstrated that graft survival was superior in recipients 40 to 49 years of age, with reduced patient survival in those 50 to 59 years of age and poor graft and patient survival in those >60 years of age .

- According to International Pancreas Transplant Registry (IPTR) data, some patients age 60 years and older may benefit from SPK transplantation.

Glomerular filtration rate (GFR)

- The national pancreas allocation system requires SPK transplant candidates to meet criteria for kidney transplant listing :
- GFR ≤20 mL/min or dialysis dependence

Insulin requirement

- Patients who are insulinopenic or who have undetectable or very low C-peptide levels are most likely to benefit from the procedure.

- In general, patients with insulin requirements exceeding 1 unit/kg/day may not always achieve euglycemia after pancreas transplant.

…Insulin requirement

- Experimentally, very high daily insulin requirement suggests that the patient may have insulin resistance or anti-insulin/islet cell antibodies; such patients may be less likely to benefit from pancreas transplantation and be rendered insulin free.

- However, patients who are on peritoneal dialysis may have large insulin requirements due to the use of dextrose-containing dialysate.

- Complications of insulin therapy, including the presence of hypoglycemic unawareness and frequency/severity of either hypoglycemic or hyperglycemic episodes, may increase the urgency for pancreas transplantation.

Body mass index (BMI)

- The maximum allowable BMI for SPK or PAK transplantation varies between centers but is often lower than that for KTA .
- **Most centers use a BMI threshold of 30 kg/m2.**
- Some centers may consider performing SPK transplants in selected patients with a BMI in the 30 to 35 kg/m2 range, whereas very few pancreas transplants are ever performed in patients with a BMI >35 kg/m2 .
- By comparison, BMI thresholds for KTA typically range from 36 to 40 kg/m2, although some centers will consider selected patients with a BMI >40 kg/m2 depending on body habitus and other associated factors.

- Patients with a very low BMI may have a higher mortality following SPK transplantation possibly because of associated conditions such as deconditioning, frailty, malnutrition, and sarcopenia .

Other criteria

- Potential recipients should be screened for :

- Tobacco and other substance use
- Functional capacity
- Presence and severity of diabetic-related complications
- Additional comorbidities

Contraindications

- Although contraindications may vary by transplant center, absolute contraindications that are adopted by most centers include:

- Age >65 years
- Non-insulin-requiring diabetes
- Body mass index (BMI) >35 kg/m2
- Advanced cardiopulmonary disease (ejection fraction below 30 percent, pulmonary artery systolic pressure >50 mmHg, or positive cardiac stress test with uncorrectable coronary artery disease)

…Contraindications

- Heavy smoking (>1 pack per day or patients with moderate-to-severe smoking-related morbidities [coronary heart disease, symptomatic or documented cerebrovascular or peripheral vascular disease, chronic obstructive lung disease, history of non-cutaneous malignancy])

- Severe peripheral vascular (aorto-iliac) disease

…Contraindications

- Moderate to severe dysfunction in other (non-kidney) organ systems (lung, liver, central nervous system [CNS]) including:

✓cirrhosis

✓portal hypertension

✓advanced chronic obstructive pulmonary disease

✓dementia

✓severe neurologic deficits

…Contraindications

- Active malignancy with the exception of nonmelanoma skin cancer or low-grade prostate cancer
- Severe local or systemic infection
- Inadequate psychosocial support and financial resources
- Active substance addiction or abuse

…Contraindications

- Major psychiatric illness that cannot be managed sufficiently to enable posttransplant care and safety
- Poor overall functional and performance status (severe deconditioning or malnutrition, frailty, dementia, wheelchair bound, need for chronic oxygen therapy)
- Chronic nonhealing wounds
- Projected life expectancy < 5 years

Relative contraindications to pancreas-kidney transplantation

- Age<18 or > 60 years
- BMI >30 to 35 kg/m
- Daily insulin requirement >1 unit/kg
- Insulin requiring <3 years
- Left ventricular ejection fraction < 40%
- Recent myocardial infarction or stroke
- Pulmonary artery systolic pressure >50 mmHg (confirmed by right heart catheterization)
- Active tobacco smoking (up to 1 pack/day or patient has mild smoking-related morbidities)
- History of major unilateral or bilateral extremity amputations
- Presence of aorto-iliac or aorto-bifemoral bypass graft
- Symptomatic cerebrovascular or peripheral vascular disease
- Positive thrombophilia screen or history of hypercoagulability
- Peritoneal dialysis with history of multiple prior episodes of peritonitis
- History of multiple previous laparotomies
- History of previous intra-abdominal/pelvic irradiation or multiple surgical procedures
- Severe or uncontrolled orthostasis or hypotension
- Severe or uncontrolled gastroparesis
- Presence of an ostomy, feeding tube, or chronic bladder drainage catheter
- History of previous substance abuse, psychiatric illness, or noncompliance/nonadherence
- Limited psychosocial support and resources (lives alone, relies on public transportation)
- Jehovah's Witness who refuses blood products

Pretransplant evaluation

- **Potential recipients are carefully screened for :**

✓Coronary heart disease

✓Congestive heart failure

✓Peripheral vascular disease

✓Active infections

✓Chronic nonhealing wounds

- The pretransplant medical evaluation for a diabetic patient is similar regardless of whether they are being considered for either a simultaneous pancreas-kidney (SPK) transplant, pancreas after kidney (PAK) transplant, or kidney transplant alone (KTA) with the exception that thrombophilia screening is performed prior to consideration for pancreas transplantation

Cardiovascular evaluation

- Cardiovascular disease remains the most common cause of death following pancreas transplantation among diabetic patients .

- Coronary heart disease, defined by prior myocardial infarction, coronary bypass, or percutaneous coronary angioplasty in the past
- All pancreas transplant candidates were screened for coronary heart disease
- Patients who have limited expected survival due to severe cardiac disease; should not undergo transplantation.

…Cardiovascular evaluation

- The optimal approach to screening is not clear.
- Most centers screen with either noninvasive tests or cardiac catheterization or both .
- Overall approach depends upon cardiovascular risk factors, including dialysis duration, duration of diabetes, and smoking history.

…Cardiovascular evaluation

- **In all candidates who are already on dialysis** and who have had diabetes >25 years, any smoking history, or other cardiovascular risk factors or disease (age >55 years, hypertension, history of myocardial infarction, congestive heart failure, low ejection fraction, valvular heart disease, arrhythmias, pulmonary hypertension, cerebrovascular disease, or previous major amputation) , refer for formal cardiology evaluation and potential cardiac catheterization.

…Cardiovascular evaluation

- **In all candidates who are not on dialysis**, have had diabetes for ≤25 years, are nonsmokers, and have no other cardiovascular risk factors, perform **noninvasive testing and reserve cardiac catheterization for those patients who have a positive noninvasive stress test.**

- Significant coronary heart disease that is not amenable to revascularization may exclude candidates from pancreas transplant consideration.

- It is important to note, however, that most diabetic patients with ESKD have identifiable cardiac and/or peripheral vascular disease.

- It is not the presence but rather the severity of the cardiovascular disease (and if it is correctable) that determines whether the patient is an appropriate candidate for pancreas transplantation.

- In patients with smoking-related morbidities (coronary artery disease, symptomatic or documented cerebrovascular or peripheral vascular disease, chronic obstructive lung disease, history of noncutaneous malignancy), complete smoking cessation is required and should be validated by urine nicotine tests prior to transplant.

- A newer contraindication is chronic severe hypotension related to severe diabetic autonomic neuropathy or chronic dialysis, either of which may result in significant and irreversible cardiac dysfunction.
- Many of these patients require the use of oral vasopressors (such as midodrine) or other agents (such as fludrocortisone) to maintain an adequate systolic pressure.
- Although some patients may manifest orthostatic hypotension (which by itself is not a contraindication)

- The inability to consistently maintain a systolic pressure above 100 mmHg places the transplanted pancreas at high risk for vascular thrombosis and the transplanted kidney at risk for ongoing ischemic damage with poor recovery of kidney function.

Evaluation of peripheral vascular disease

- Peripheral vascular disease is common among diabetic patients with ESKD and may prevent successful transplantation of either the kidney or pancreas because of technical and hemodynamic considerations.

- Careful examination of iliac and peripheral pulses should be done in all patients.

…Evaluation of peripheral vascular disease

- To identify patients with iliac calcifications, we screen all diabetic patients with a noncontrast abdominopelvic computed tomography (CT) scan who:

✓ Older than 45 years of age

✓ Those with longstanding hypertension

✓ Those with poor femoral pulses or evidence of vascular disease elsewhere (eg, coronary heart disease or cerebrovascular disease)

❖ Many centers screen all diabetic pancreas transplant candidates with a non-contrast CT scan.

…Evaluation of peripheral vascular disease

- In addition, many centers will perform carotid and iliac artery duplex ultrasonographic imaging as part of the standard evaluation for transplantation in this patient population.
- The diagnosis of peripheral vascular disease is difficult to establish in such patients because of the presence of medial artery calcifications that render vessels noncompressible for a standard ankle brachial index and/or toe brachial index.
- Patients with symptoms of peripheral vascular disease (eg, claudication), diminished pulses on exam, or abnormal imaging are referred to a vascular specialist for further assessment and testing

Hypercoagulability evaluation

- In contrast to KTA, the risk of pancreas thrombosis is relatively high because it is a low microcirculatory flow organ with its blood supply based on collateral circulation.
- Consequently, patients with a history of thrombophilia (hypercoagulability) or those on anticoagulation represent a unique risk factor for early pancreas graft loss.
- In addition, diabetes may be associated with a prothrombotic state .
- For these reasons, we recommend thrombophilia screening on all potential pancreas transplant recipients with the selective use of perioperative anticoagulation to reduce the risk of early thrombosis.

Cancer screening

- Malignancy in the past two years, with the exception of cutaneous squamous, basal cell tumors, and early prostate cancer with low Gleason score, is another contraindication .

- In cases of localized and treated cancer, the cancer-free interval will depend upon the stage and type of cancer.

- Consultation and "clearance" may need to be obtained from an oncology specialist, but ultimately a determination will need to be made if the patient's mortality in the absence of transplantation is predicted to be higher than their risk of recurrence.

- Standard cancer screening for SPK or PAK transplantation is similar to KTA and may include:

- Chest radiography
- Mammography
- Gynecologic examination
- Dermatology assessment (particularly with any history of skin cancer)
- Colonoscopy
- Prostate-specific antigen testing

Infectious disease evaluation

- Incurable or incompletely treated or unresolved active or chronic infections represent another contraindication and may include chronic active hepatitis B, hepatitis C, and uncontrolled HIV.

- In the absence of cirrhosis, adequately treated hepatitis B (hepatitis B surface antigen [HbsAg] negative) or hepatitis C virus are no longer considered contraindications to transplantation.
- In the case of hepatitis C viral infection without cirrhosis, transplantation may precede treatment for hepatitis C to take advantage of organs from hepatitis C-positive donors and provided that the patient has been accepted as a good candidate for anti-hepatitis C virus treatment.

- HIV-infected patients with adequately controlled HIV infection, characterized by:

- CD4 count >200
- Undetectable HIV RNA levels
- Stable antiretroviral regimen for a minimum of three months
- Absence of opportunistic infections in the past 12 months

May be considered acceptable for pancreas transplantation.

- Patients with chronic nonhealing wounds or osteomyelitis are not considered appropriate for transplantation.

Psychosocial evaluation

- An adequate support system with requisite resources is needed to ensure the success of transplantation.
- Abstinence from all illicit drugs for a minimum of six months and documentation of compliance are necessary.
- Smoking cessation is strongly encouraged and at some centers is an absolute requirement.
- Social alcohol and medicinal marijuana use are considered acceptable, but overuse/dependency/abuse is a contraindication.
- Well-controlled psychiatric disorders are another risk factor that warrant further evaluation, if necessary, by a mental health specialist

Functional assessment

- Severe frailty, deconditioning, malnutrition, and sarcopenia are relative contraindications to transplant

- This frailty instrument generates a numerical score that categorizes patients as fit, intermediately fit, or frail.

- In an analysis of data from the Scientific Registry of Transplant (SRTR) between 2006 and 2019, the risk of mortality progressively increased for SPK transplant recipients, requiring assistance, and who are disabled, compared with that of patients with normal functioning

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