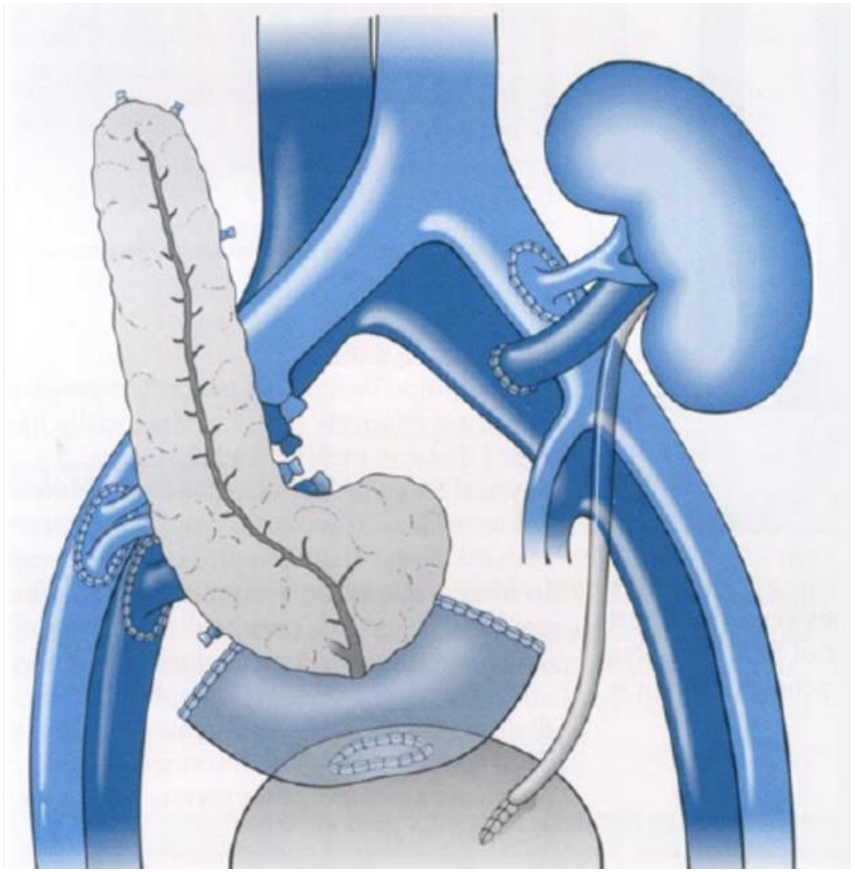

Simultaneous Pancreas & Kidney Transplantation

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Outlines

- Epidemiology of pancreases- kidney transplantation
- Benefits of SPK
- Who are suitable cases for SPK? Contraindications?
- Pretransplant evaluations
- SELECTION OF OPTIMAL PROCEDURE
- Complications
- Management of SPK

EPIDEMIOLOGY

- > 68,000 pancreas transplants were performed worldwide between 1966 - 2024.
- In the USA during 2023:
- 914 pancreas transplants
  - 809: simultaneous pancreas-kidney (SPK) transplants
  - 26: pancreas transplantation alone (PTA)
  - 35: sequential pancreas after kidney (PAK) transplants
  - 44: pancreas transplants: as multi-organ transplants that did not include a kidney.

EPIDEMIOLOGY in IRAN

- Centers:
- Shiraz: The first PT (in the form of SPK) in the Middle East has been performed by Dr. Nikeghbalian at the Shiraz Organ Transplantation Center.
  - From 2006 to 2021: 268 procedure
- Tehran: Imam Khomeini Hospital
- Mashhad: Montaserieh Transplant Hospital

Benefits of SPK

- Major benefits: Decreased mortality and improved quality of life.
- Patient survival
  - Among patients with type 1 diabetes, SPK transplantation appears to confer better survival than KTA, at least when compared with deceased-donor KTA
- Kidney allograft survival
  - Although pancreas transplantation is associated with a finite risk (5%) of early graft failure (usually secondary to thrombosis) the mean graft longevity in the absence of early graft loss (conditional graft survival) is 14 years for both the kidney and pancreas grafts following SPK transplantation

Other potential benefits

- Glucose metabolism
- Lipid metabolism
- *Diabetic kidney disease*
- Retinopathy
- Circulation
- Fertility
- Fracture risk

Patient selection

- The vast majority of SPK and PAK transplants are performed in patients with **type 1 diabetes**, although an increasing number are performed in patients with a type 2 diabetes phenotype.

Patient selection

- *Characterization of type 2 diabetes phenotype:*
  - 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
  - Lack of autoimmune markers of diabetes
  - Absence of diabetic ketoacidosis
  - History of obesity

Patient selection

- Potential SPK and PAK transplant candidates with non-type 1 diabetes usually meet the following selection criteria:
  - Age <60 years
  - BMI <30 kg/m^2
  - Insulin requiring for a minimum of 3 years with a total daily insulin requirement <1 unit/kg/day
  - Fasting C-peptide level <10 ng/mL
  - Presence of complicated or hyperlabile diabetes

Patient selection

- Higher pretransplant C-peptide levels:
  - Worse prognosis
  - Associated with greater posttransplant weight gain

- Patients with **extreme insulin resistance** may not be appropriate candidates for pancreas transplantation

Patient selection

- Individual centers may have other cut-offs for SPK or PAK candidate exclusion: such as age>50 years or BMI >28 kg/m^2.
- Alternatively, other centers may transplant patients up to 65 years of age and with a BMI of 30 to 35 kg/m^2 .

Iranian guideline

۱- دیابت نوع اول با نارسایی کلیه(GFR<20 mL/min یا بیمار دریافت کننده دیالیز مزمن) : در این مورد حداقل ۲ ماه از کاهش GFR بدون بهبودی بگذرد و یا بیمار تحت درمان با دیالیز مزمن (اعم از همودیالیز یا دیالیز صفاقی) باشد و هم چنین حداقل ۵ سال از دیابت نوع اول گذشته باشد.

۲- دیابت نوع دو در صورت داشتن شرایط زیر:

- ✓ سن کمتر از ۵۰سال
- ✓ BMI <30 kg/m2
- ✓ نداشتن مشکل قلبی، عروقی
- ✓ نیاز به انسولین کمتر از 1 unit/kg/day
- ✓ وجود نفروپاتی

۳- بیماران مبتلا به سیستیک فیبروزیس و یا پانکراتیت مزمن کلسیفیه و یا پانکراتیت مزمن اتوایمیون که عملاً ،لوزالمعده در آن شرایط کارایی مفیدی نداشته باشد

٤-بیماری فیبروز کیستیک پانکراس و سایر بیماریهای مادرزادی شامل آژنزی پانکراس

۵-- تومورهای بدون متاستاز پانکراس با انهدام کل عضو

CONTRAINDICATIONS

- Age >65 years
- Non-insulin-requiring diabetes
- BMI>35 kg/m2
- Advanced cardiopulmonary disease (EF<30%, pulmonary artery systolic pressure >50mmHg, or positive cardiac stress test with uncorrectable coronary artery disease)
- 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, COPD, history of non-cutaneous malignancy)

CONTRAINDICATIONS

- Severe peripheral vascular (aorto-iliac) disease
- Moderate to severe dysfunction in other (non-kidney) organ systems (lung, liver, CNS) including cirrhosis, portal hypertension, advanced COPD, dementia, or severe neurologic deficits,
- 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

CONTRAINDICATIONS

- Active substance addiction or substance use disorder
- 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 user, need for chronic oxygen therapy)
- Chronic nonhealing wounds
- Projected life expectancy <5 years

Iranian guideline

۱- موارد منع پیوند همانند بقیه پیوند ارگانهای جامد می باشد.

- ✓ اعتیاد به موارد مخدر، الکل
- ✓ عفونت فعال
- ✓ مشکلات روانی
- ✓ عدم حمایت خانواده

۲- مشکلات قلبی- عروقی پیشرفته ناشی از پیشرفت دیابت

۳- نداشتن عروق مناسب جهت پیوند

٤- BMI>30 kg/m2

٥- سن کمتر از ۱۸سال و بیش از ۵۰سال

٦- بیماری شدید کبدی

Iranian guideline

معیار های انتخاب اهدا کننده مناسب

۱- سن ۳-۴۵ سال

۲- BMI<25 kg/m2

۳- بستری در ICUکمتر از ۵روز

٤- نیاز به اینوتروپ با دوز کم

۵- Ischemic Time<12 h

PRETRANSPLANT EVALUATION

- Cardiovascular evaluation: the single most important clinical aspect of recipient selection is the overall assessment of cardiovascular risk, burden, and reserve.
- Refer for formal cardiology evaluation and potential **cardiac catheterization**:
  - Dialysis patients
  - Diabetes >25 years
  - Any smoking history
  - Other cardiovascular risk factors or disease (age >55 years, HTN, history of MI, CHF , low EF, valvular heart disease, arrhythmias, pulmonary hypertension, cerebrovascular disease, or previous major amputation)

PRETRANSPLANT EVALUATION

- *Noninvasive testing :*
  - *In all candidates who are not on dialysis*
  - *diabetes for ≤25 years*
  - *Nonsmokers*
  - *No other cardiovascular risk factors*
- *For patients who are able to exercise and achieve 85 % maximum heart rate, we use an exercise stress test.*

PRETRANSPLANT EVALUATION

- A newer contraindication: **chronic severe hypotension** related to severe diabetic autonomic neuropathy or chronic dialysis
- Many of these patients require the use of oral vasopressors (such as midodrine) or other agents (such as fludrocortisone).
- Although some patients may manifest orthostatic hypotension (which by itself is not a contraindication), the inability to consistently maintain SBP>100 mmHg
  - 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

- Careful examination of iliac and peripheral pulses should be done in all patients.
- To identify patients with iliac calcifications: noncontrast abdominopelvic CT scan in:
  - > 45 years of age
  - Longstanding hypertension
  - 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 noncontrast CT scan.
- Carotid and iliac artery duplex ultrasonographic imaging as part of the standard evaluation for transplantation in this patient population.

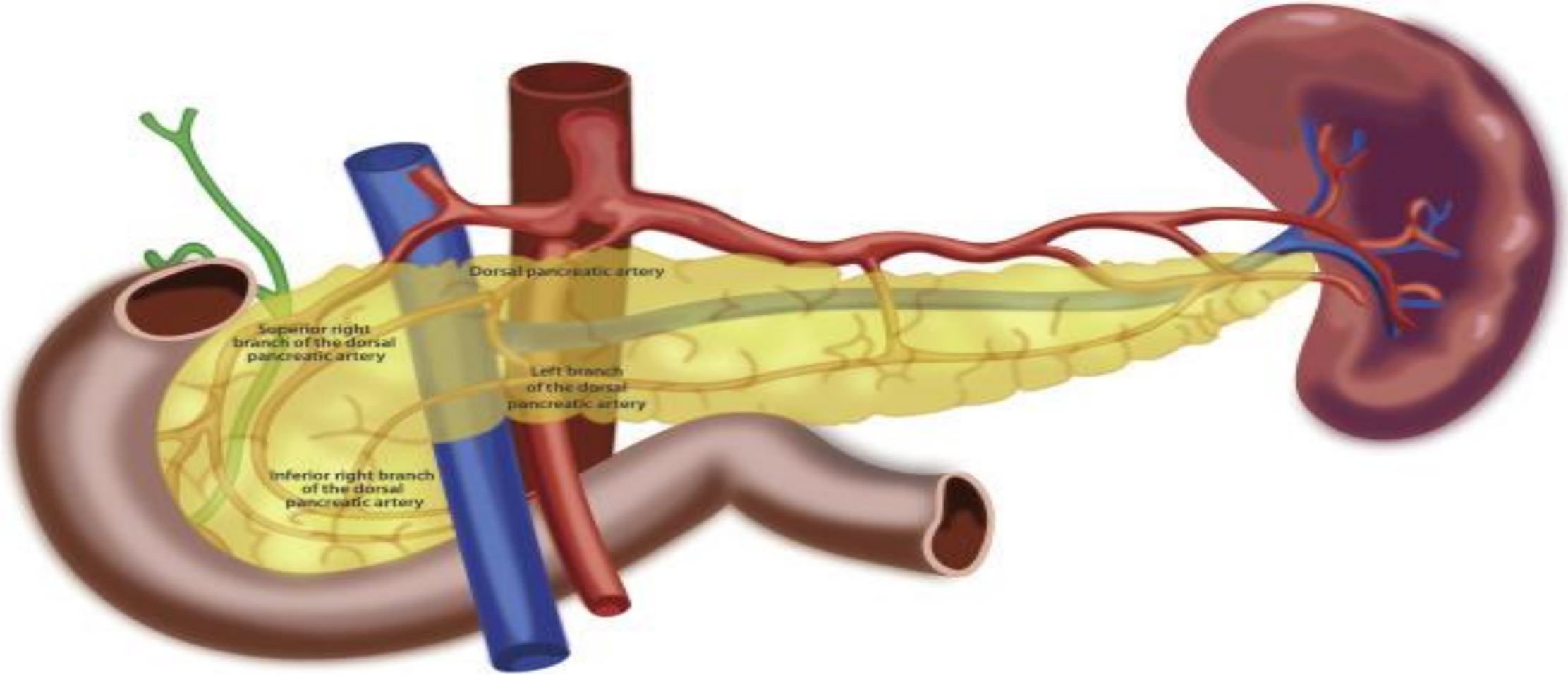
Hypercoagulability evaluation

- 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.
- Patients with a history of thrombophilia (hypercoagulability) or those on anticoagulation: a unique risk factor for early pancreas graft loss.
- Diabetes may be associated with a prothrombotic state.
- Recommendation: **thrombophilia screening on all potential pancreas transplant recipients with the selective use of perioperative anticoagulation to reduce the risk of early thrombosis**.

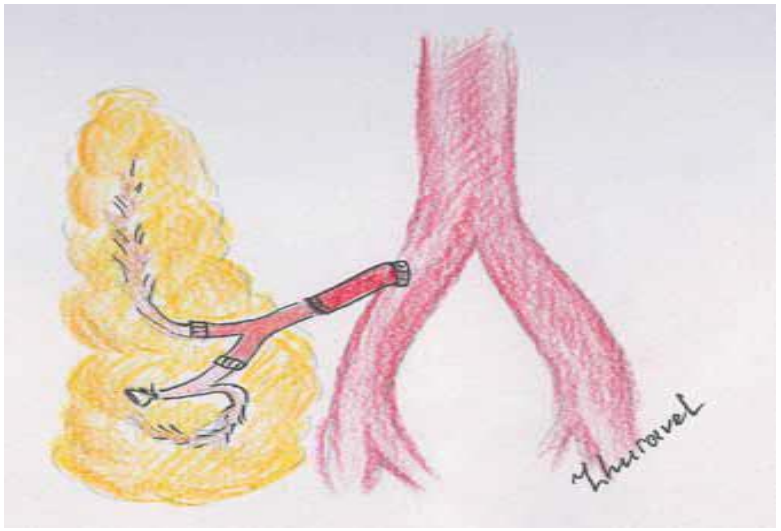
Other Evaluations

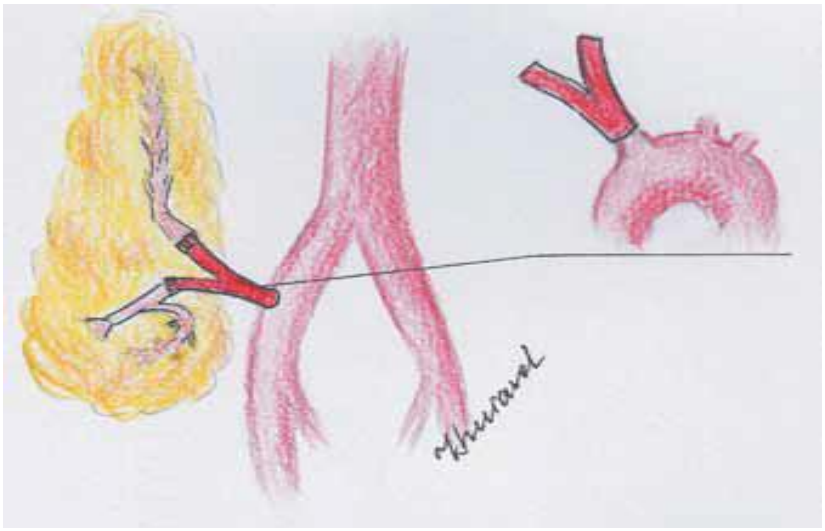
- Cancer screening
- Infectious disease evaluation
- Psychosocial evaluation
- Functional assessment

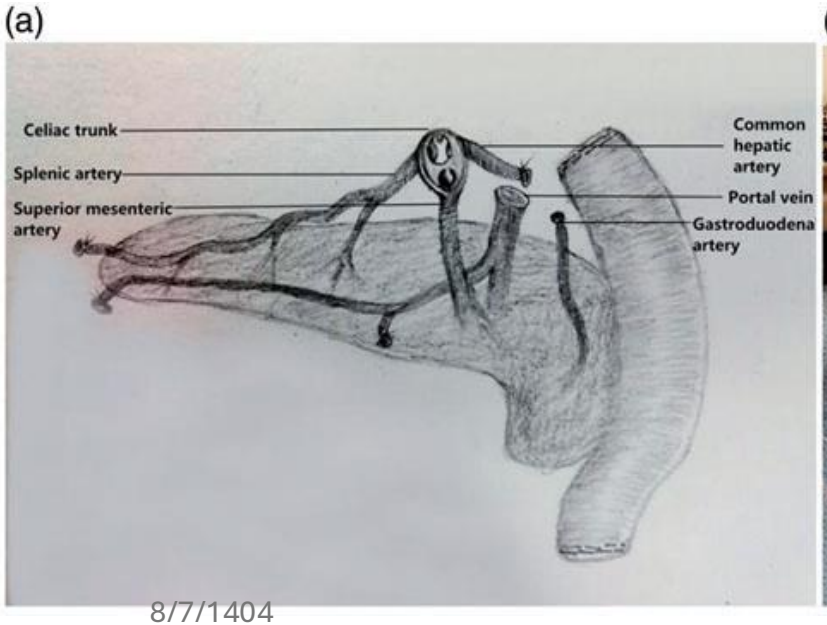
Surgical technique

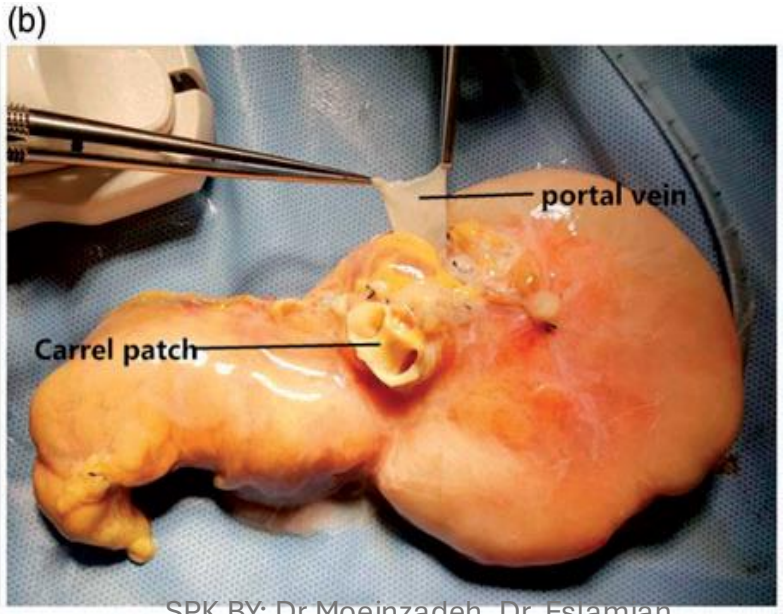


Arterial anastomosis

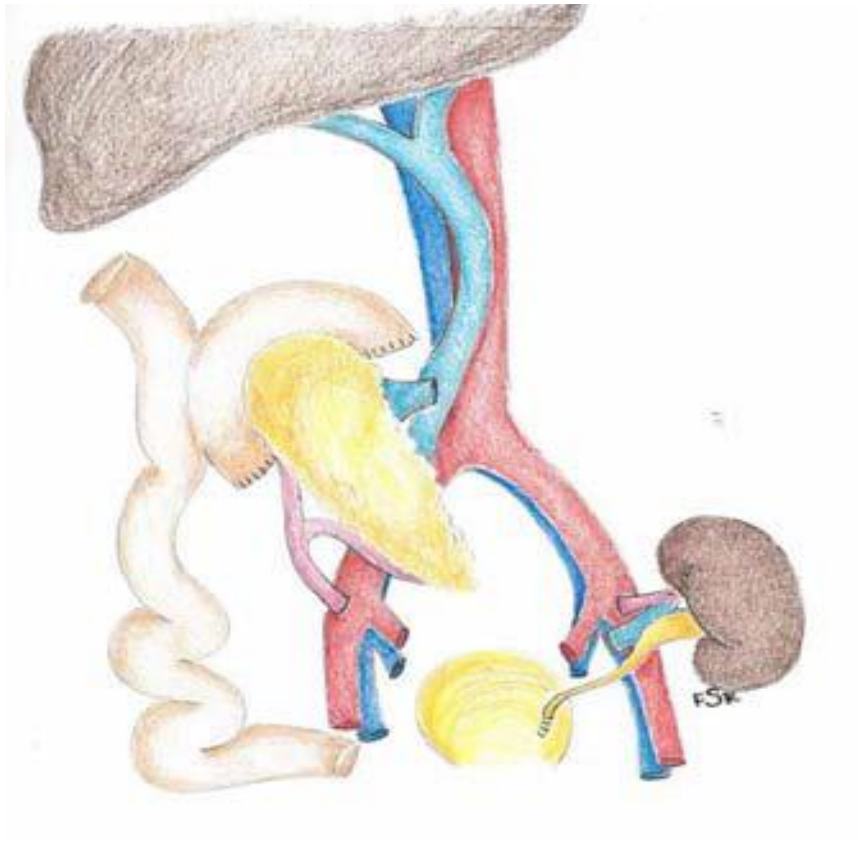


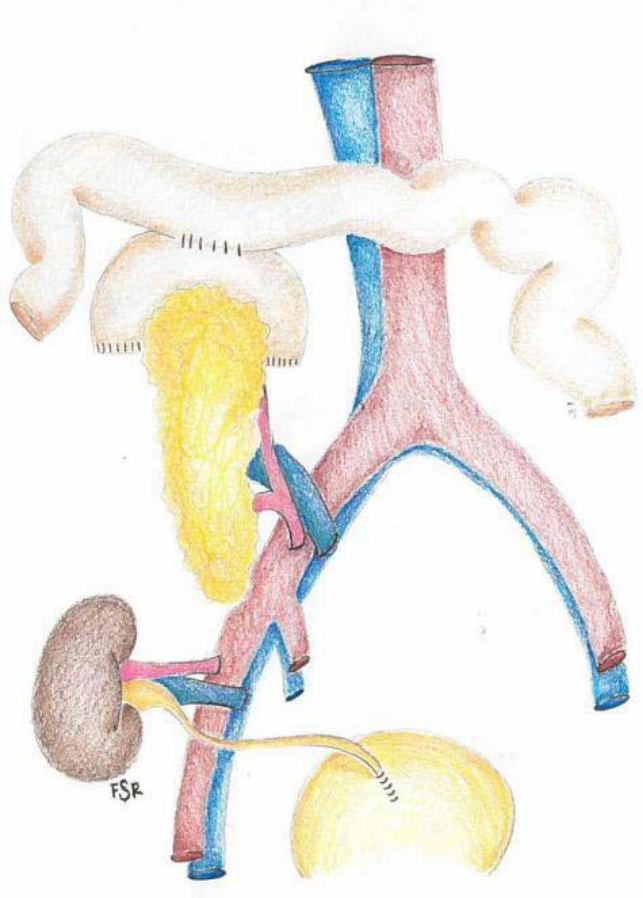






Venous anstamosis.systemic/portal





- Venous effluent can be drained via the portal vein or the systemic circulation;
- glycemic control and total cholesterol
- graft survival. No differences in complications were seen when exocrine drainage was enteric for the systemic venous group.
- Fasting insulin was significantly lower within the portal drained group; however, fasting blood glucose levels (-3.4 mg/dL, p = 0.32) and hemoglobin A1C levels (mean difference 0.124%, p = 0.25) were comparable.
- Total cholesterol levels and other measures of lipids, showed no difference.
- Based on this systematic review and meta-analysis, there is no evidence of differences in outcomes or metabolic control

-
- | Feature | Portal Venous Drainage | Systemic Venous Drainage |
- |---|---|---|
- | Venous outflow | Into portal system via SMV | Into systemic veins (iliac veins, IVC)|
- | Physiologic similarity | More physiological (to liver) | Less physiological, bypasses liver |
- | Immunologic response | Lower rejection rates, milder rejection | Higher rejection rates, more severe rejection |
- | Graft survival | Slightly better, especially in PAK | Comparable overall patient and graft survival|
- | Technical considerations | More complex, anatomic limitations | Technically easier, preferred in obesity or prior transplant|
- | Metabolic effects | Better insulin metabolism, decreased mtabolic abnormalities | More metabolic disturbances possible |

Systemic Venous Drainage (SVD):

- Indicated when portal vein or superior mesenteric vein anatomy is unfavorable or unavailable due to thrombosis, fibrosis, or prior surgeries.

- Preferred in obese recipients or those with difficult portal venous access.

- Easier to perform technically, especially in the iliac veins or inferior vena cava as outflow veins.

- Used as an alternative when portal drainage is not feasible or safe.

Immunological Benefit :Patients may benefit from reduced rejection risk due to hepatic immune processing of donor antigens experience better (portal)

Recipients , Pancreas After Kidney (PAK) or Pancreas Transplant Alone (PTA): PVD shows a more pronounced survival benefit and lower rejection rates .

Early and late complication

- ***Major Complications***
- HEMORRHAGE:which can be as high as 30%. Bleeding represents less than 0.3% of early
- pancreatic graft losses
- Blood glucose monitoring in the early post-transplant period is especially useful to warn us about a possible vascular complication.
- Graft thrombosis: The most frequent and serious complication, potentially leading to graft failure in 3.7%-5.9% of cases. It can affect arterial or venous supply and often requires urgent intervention or graft removal . Thrombosis can be partial or total. Venous thrombosis has a higher incidence than arterial thrombosis.
- Early ,within the first 48 h after the surgery.presented; Early complete venous graft thrombosis manifests as hyperglycaemia, abdominal Pain
- plus melena when the drainage is enteric or haematuria and decrease in urinary-amylase production when the drainage is to the bladder
- Arterial thrombosis, Reintervention and pancreatectomy may be the best option on many occasions

Early and late complication

- Graft pancreatitis; Common after pancreas transplant, may occur early (within 3 months) or later. It can lead to graft inflammation, necrosis, or be a precursor to vascular thrombosis.
- Imaging (CT) helps distinguish severity. Early pancreatitis after a pancreas transplant occurs in 10%-20% of patient. associated to ischemia-reperfusion damage. acute rejection and technical problems
- High serum amylase levels and graft edema are characteristic.
- Most ischemia reperfusion pancreatitis are mild and progress favourably in the first days. ischemia-reperfusion damage occurs within the first 24-48 h after transplantation and rapidly evolves towards normalization[
- Pancreatitis due to acute rejection usually results in a later elevation of serum amylase, from the fifth day after the transplantation. They are usually accompanied by data on acute rejection in the renal graft.

Early and late complication

- Severity of pancreatitis is defined by laboratory data, including leukocytosis, hypocalcemia and elevated C-reactive protein.
- Enteric or pancreatic leaks: Around 2.5%-2.9% experience leaks at the duodenojejunal anastomosis, causing peritonitis, fluid collections, abscesses, and increasing graft loss risk. These usually require surgical re-exploration .
- Infections and abscesses: Surgical wound infections, intra-abdominal collections (seromas, hematomas, lymphoceles), and peripancreatic fluid collections are common and need management with antibiotics or drainage .

Risks of Venous Thrombosis:

- Predisposing factors include the hypercoagulable state common in diabetic renal failure
- technical errors like tension or torsion of vascular pedicles, and low venous flow velocity increase thrombosis risk.
- Post-reperfusion pancreatitis significantly raises the risk.
- Hypotension during and after surgery, especially systolic blood pressure below 95 mm Hg, is another risk factor.
- Venous thrombosis occurs more frequently than arterial thrombosis with an incidence of 3% to 10% for complete thrombosis, and partial thrombosis can be as high as 25-30%

Future?

- Islet cell transplant:
- Diabetes Type Primarily Type 1 diabetes with severe hypoglycemia and unstable control.
- Duration of Diabetes >5 years
  Age Adults (18-64 years typical), some centers may use stricter criteria
- Unstable glucose control despite optimal insulin therapy Body Weight/BMI Usually <75 kg for males, <70 kg for females (some programs use BMI <27-30)
  Kidney Function Creatinine <1.5 mg/dL, proteinuria <300 mg/day Often with good renal
- Presence of cardiovascular disease may exclude whole pancreas transplant but not ICT
- Significant cardiac or vascular disease usually contraindicates pancreas transplant due to surgical risks

- Stem cell TX

- Artificial pancreas

- Diabetes Type Primarily Type 1 diabetes with severe hypoglycemia and unstable control.
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- Presence of cardiovascular disease may exclude whole pancreas transplant but not ICT
- Significant cardiac or vascular disease usually contraindicates pancreas transplant due to surgical risks

Other complications

- **Infections:**
- **CMV infection** is among the most common viruses causing clinically significant infection in SPK recipients.
- **BK virus** may be a significant cause of kidney graft loss in SPK

- **Metabolic disturbances**

Induction Therapy

- T cell-depleting antibodies (such as polyclonal rabbit antithymocyte globulin [**rATG]-Thymoglobulin** and
- Monoclonal **Alemtuzumab** [anti-CD52 antibody]) and
- Nondepleting antibodies such as interleukin (IL)-2 receptor antibodies (monoclonal **Basiliximab**).

Induction Therapy:

- rATG-Thymoglobulin 1-1.5 mg/kg intraoperatively followed by 1.5 to 2 mg/kg of rATG-Thymoglobulin per day for the next two to three days for a total cumulative induction dose of 4.5 to 6 mg/kg.
- If rATG Thymoglobulin cannot be given, Alemtuzumab

In patient care for SPK patients

The major early management issues are:

1. **Potential for bleeding.**
2. **Fluid balance** – these patients in generally require larger volumes of fluid than kidney transplantation alone.
3. **Blood Glucose control** – pancreatic function will dramatically reduce previous insulin requirements. Check for hypoglycaemia
4. **Electrolyte disturbance.**

Fluid management

- All patients need a background fluid infusion; we would suggest 20mls/hour of 10% dextrose for anuric patients
- Once patients fasting: should go on to a sliding scale insulin.
- **Day 2 post transplant**

Crystalloid at urine output + 60 mls/hour.
Aim for CVP 5-11 cm H2O. If CVP low then give colloid (4.5% HAS 200 ml aliquots) or crystalloid. **However it should be noted that SPK patients are likely to require more IV fluid than patients who have undergone kidney transplant alone.**

In patient care for SPK patients

- Repeat U&Es, Glucose, FBC, LFT, Serum and drain Amylase daily

DVT prophylaxis	heparin 5000 units sc bd
GI prophylaxis	Ranitidine 50mg tds
IV Fluid	Initially crystalloid at urine output + 60mls/hr
	200mls bolus if clinical signs of hypovolaemia
	NEEDS REGULAR CLINICAL REVIEW

Initiation of Maintenance Therapy

- Because recipients of a pancreas transplant are typically NPO for the first few days after surgery, maintenance immunosuppression during this period is generally administered IV or per nasogastric tube until patients are able to take oral medications.
- Alternatively, tacrolimus may be given sublingually as a powder.

Maintenance Therapy

- ▶ Maintenance therapy is similar for patients receiving an SPK or PAK transplant and typically includes:
  - a calcineurin inhibitor (**Tacrolimus**)
  - an antimetabolite (**Mycophenolate**) or (mTOR) inhibitor
  - a tapering dose of glucocorticoids (**Prednisone**)

- ▶ This approach is generally preferred by most transplant centers, although practice may vary from center to center.

Maintenance Therapy

- Administration of tacrolimus on the evening of postoperative day1: immediate-release tacrolimus 1 to 2 mg twice daily, with doses adjusted to achieve a 12-hour trough level of 8 to 10 ng/mL for the first three months post-transplant and 6 to 8 ng/mL thereafter.
- OR
- Extended-release tacrolimus tablets on postoperative day 1 at 0.08 mg/kg once per day.

Maintenance Therapy

- Administration of mycophenolate mofetil (MMF) 1000 mg IV twice daily or MMF liquid suspension 1000 mg twice daily per nasogastric tube starting on postoperative day 1. When the patient is able to take oral medications by mouth (typically on postoperative day 2 or 3), we switch from IV or liquid suspension MMF to either enteric-coated.

Maintenance Therapy

- IV **methylprednisolone** at 7 mg/kg (maximum of 500 mg) in the operating room followed by IV methylprednisolone 20 mg daily until the patient is able to take medications by mouth.
- Switch IV methylprednisolone to oral prednisone (20 mg once daily for the first week after transplantation, then tapered to 5 mg daily by one to two months posttransplant.

Maintenance Therapy

- mTOR Inhibitors:
- **Sirolimus** is administered once daily because of a long half-life, and **everolimus** is administered twice daily; both agents are dosed to achieve target trough levels of 3 to 8 ng/mL .
- The role of mTOR inhibitors may be better suited to replace an antimetabolite rather than a calcineurin inhibitor, which may then permit glucocorticoid weaning and withdrawal.

Maintenance Therapy

- There was no difference in NODAT incidence between patients treated with CNI or mTOR inhibitors

SPK monitoring

Monitoring the pancreas graft: low sensitivity and specificity for rejection