Pancreatic transplantation: Brief review of the current evidence

Ahmed Aref, Tariq Zayan, Ravi Pararajasingam, Ajay Sharma, Ahmed Halawa

ORCID number: Ahmed Aref (0000-0003-4184-3883); Tariq Zayan (0000-0001-9140-0795); Ravi Pararajasingam (0000-0002-8800-537X); Ajay Sharma (0000-0003-4050-6586); Ahmed Halawa (0000-0002-7305-446X).

Ahmed Aref, Tariq Zayan, Department of Nephrology, Sur Hospital, Sur 411, Oman

Ahmed Aref, Tariq Zayan, Ravi Pararajasingam, Ajay Sharma, Ahmed Halawa, Faculty of Health and Science, Institute of Learning and Teaching, University of Liverpool, Liverpool L69 3GB, United Kingdom

Ravi Pararajasingam, Department of Transplantation, Sheffield Teaching Hospitals, Sheffield S5 7AU, United Kingdom

Ajay Sharma, Renal Medicine, Royal Liverpool University Hospitals, Liverpool L7 8XP, United Kingdom

Ahmed Halawa, Department of Transplantation Surgery, Sheffield Teaching Hospitals, Sheffield S5 7AU, United Kingdom

Corresponding author: Ahmed Halawa, FRCS (Gen Surg), FRSC, MD, MSc, Surgeon, Department of Transplantation Surgery, Sheffield Teaching Hospitals, Herries Road, Sheffield S5 7AU, United Kingdom. ahmed.halawa@sth.nhs.uk
Telephone: +44-7787-542128
Fax: +44-1142-714604

Abstract

Kidney transplantation is the treatment of choice for management of end-stage renal disease. However, in diabetic patients, the underlying metabolic disturbance will persist and even may get worse after isolated kidney transplantation. Pancreatic transplantation in humans was first introduced in 1966. The initial outcome was disappointing. However, this was changed after the improvement of surgical techniques together with better patient selection and the availability of potent and better-tolerated immune-suppression like cyclosporine and induction antibodies. Combined kidney and pancreas transplantation will not only solve the problem of organ failure, but it will also stabilise or even reverse the metabolic complications of diabetes. Combined kidney and pancreas transplantation have the best long term outcome in diabetic cases with renal failure. Nevertheless, at the cost of an initial increase in morbidity and risk of mortality. Other transplantation options include pancreas after kidney transplantation and islet cell transplantation. We aim by this work to explore various options which can be offered to a diabetic patient with advanced chronic kidney disease. Our work will provide a simplified, yet up-to-date information regarding the different management options for those diabetic chronic kidney failure patients.

Key words: Combined kidney pancrease transplantation; Renal transplantation; Diabetic kidney disease; Diabetes mellitus

Core tip: Kidney transplantation is the treatment of choice for end-stage renal disease. Combined kidney-pancreas transplantation provides the patients with the highest long term survival. There are different surgical approaches for combined kidney-pancreas transplantation with recognised advantages and limitations of each technique. Islet cell transplantation is a minimally invasive treatment option but carries a risk of sensitisation to a wide range of human leukocyte antigen antigens.

INTRODUCTION

Diabetes mellitus (DM) is the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide[1]. Successful pancreas transplantation provides optimisation of glucose metabolism for diabetic patients[2]. The current management options for diabetic patients with advanced CKD are summarised in Figure 1.

Pancreas transplant alone (PTA) is another option for managing diabetic patients with normal renal function. Moreover, transplantation of the islets of Langerhans is a promising alternative to whole pancreas transplantation which can provide adequate glycemic control without exposing the recipient to major surgical interventions[2].

DIABETIC ELIGIBILITY CRITERIA FOR TRANSPLANTATION

Diabetes is classified into two main subtypes, type 1 and type 2, based on the American Diabetes Association classification system. The discrimination between the two types of DM may be difficult in many cases[3]. Table 1 summaries the main characteristics of type 1 and type 2 DM in children and adolescents[4].

Pancreas transplantation is offered primarily to type 1 diabetic CKD patients, an approach that was supported by the fact of absence of endogenous insulin and normal insulin sensitivity. However, some cases with insulin-dependent type 2 diabetes in the United States have been accepted on simultaneous pancreas-kidney (SPK) waiting list if their body mass index (BMI) is less than 30 kg/m^2, requiring insulin, but < 1.5 U/kg per day. About 6% only of SPK waiting list cases are type 2 DM[2]. The plan for transplan-tation modality is simplified in Figure 2.

MANAGEMENT OPTIONS FOR DIABETIC PATIENTS WITH ADVANCED CKD

In advanced CKD, Preemptive kidney transplantation from a living donor will offer the patient the highest patient survival rate at five years reaching up to 91% (compared to 84% for non-extended-criteria donor transplant, and 70% for extended-criteria donor transplants)[5]. Nevertheless, this management option will not usually solve diabetes-related medical condition (as DM control may be impaired if steroids were used post kidney transplantation either as maintenance therapy or for treatment of rejection episodes)[1,2].

In the United Kingdom, the national five-year patient survival is 88% for SPK recipients, and 78% for pancreas only transplant recipients. Pancreas allograft survival rate at five years is 75% for SPK recipients and 45% pancreas-only transplants[6].

A retrospective analysis of long-term survival of 18549 patients with type 1 DM in the United States has demonstrated that the patient survival at eight years for SPK recipients was similar to living-donor kidney recipients (about 72%) while the survival for cadaveric kidney recipients was only 55%[7]. SPK is associated with significantly elevated early mortality risk most probably secondary to the surgical procedure itself, and the related complications, which result in prolonged and recurrent hospitalisation is the first few months post-transplantation[1,7]. On the other
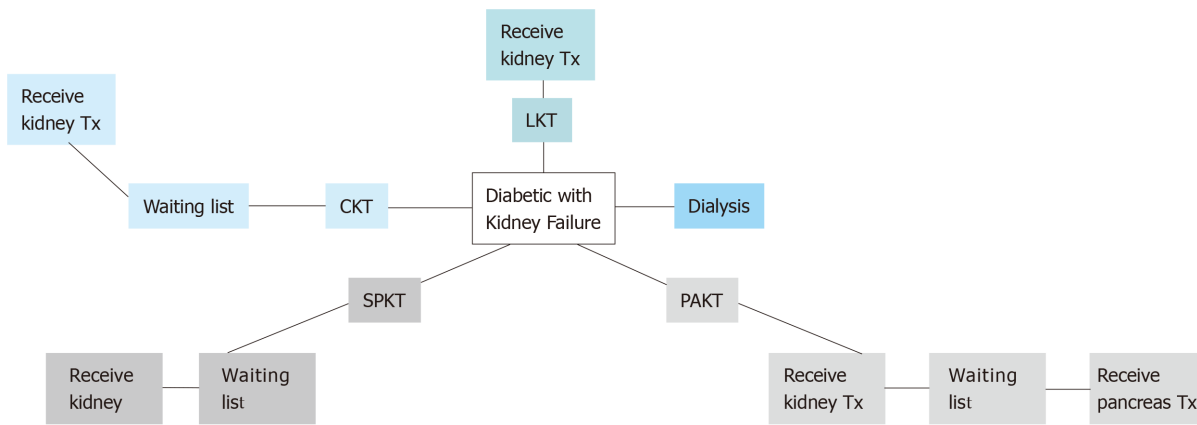
Figure 1 Options for diabetic patients with kidney failure. LKT: Living kidney transplantation. CKT: Deceased kidney transplantation; SPKT: Simultaneous pancreas and kidney transplantation; PAKT: Pancreas after kidney transplantation.

hand, the long-term outcome for SPK is better than any other transplantation option in diabetic patients[1,7]. Recent data regarding kidney allograft survival with various types of kidney pancreas transplantation are summarized in Table 2[8].

The kidney outcomes for pancreas after kidney (PAK) were from the time of pancreas transplant, which may explain the lower survival rates compared to those of SPK recipients[8]. The maintenance of a functioning pancreas allograft was associated with the favourable long-term outcome with SPK most probably secondary to stabilisation or even improvement of most of the DM associated systemic complications as illustrated in Table 3.

Data collected from 20,854 pancreas transplant recipients between 1996 and 2012 by the United Network for Organ Sharing (UNOS) was analysed for patient and graft survival[16]. The best graft survival outcome was observed in recipient ranged between 40-49 years old. Additionally, the study documented an inverse relationship between recipient age and patient survival, with reduced patient survival in those who are older than 50 years[16].

SURGICAL IMPLANTATION TECHNIQUES

In SPK operation, the kidney is usually transplanted into the left iliac fossa by the traditional approach using the iliac vessels for vascular anastomosis[2]. There are several options for pancreatic implantation reflecting the fact that there is no standard optimal technique, each surgical option has its advantages as well as disadvantages. One of the challenges is the exocrine and endocrine drainage of the pancreatic allograft[2]. The various pancreatic implantations techniques are simplified in Figure 3[2,3,17,18], while the possible complications of pancreatic transplantation were summerized in Table 4[19].

PRETRANSPLANT ASSESSMENT

The patient evaluation should follow the local protocol for transplant candidate. This includes detailed medical, surgical, and psychosocial history; a meticulous physical examination; and laboratory evaluation. However, the pretransplant workup should be very strict to identify any possible undiagnosed condition related to DM that will negatively affect the outcome. Particular attention should be given for assessing cardiovascular status and the presence of peripheral vascular disease[20].

Pancreatic transplantation is associated with an increased risk of mortality in the early post-operative period, and the most frequent cause of death is of cardiovascular event[20]. There is no universally standardised cardiovascular screening protocol for asymptomatic CKD patients[21]. Some of the internationally published protocols are illustrated in Figure 4[21].

The initial cardiac assessment could be suggested by myocardial perfusion imaging (MPI) together with exercise-based (+/- dobutamine) stress test, and results should be interpreted by an expert cardiologist[21]. Myocardial perfusion studies provide valuable information regarding functional capacity, the extent of myocardial viability, and the extent of stress-induced ischemia as well as the degree of stress defect

Table 1 Comparison of criteria of type 1 and type 2 diabetes mellitus[4]

	Type 1 diabetes	Type 2 diabetes
Prevalence	Common, increasing	Increasing
Age at presentation	Throughout childhood	Puberty
Onset	Typically, acute severe	Insidious to severe
Ketosis at onset	Common	5% to 10%[1]
Affected relative	5% to 10%	75% to 90%
Female: male	1:1	Approximately 2:1
Inheritance	Polygenic	Polygenic
HLA-DR3/4	Strong association	No association
Ethnicity	Most common in non- Hispanic white	All[2]
Insulin secretion	Decreased/absent	Variable
Insulin sensitivity	Normal when controlled	Decreased
Insulin dependence	Permanent	Variable
Obese or overweight	20% to 25% overweight[3]	> 80% obese
Acanthosis nigricans	12%[4]	50% to 90%[4]
Pancreatic antibodies	Yes[5]	No[6]

[1]Reported frequency of ketonuria or ketoacidosis at time of diagnosis of type 2 diabetes mellitus (T2DM) varies widely.
[2]In North America, T2DM predominates in native America, African-American, Hispanic, Canadian First Nation, Pacific Islander, and Asian-American youth.
[3]With increased prevalence of childhood overweight, 20% to 25% of newly diagnosed with type 1 diabetes mellitus (T1DM) are overweight, which is higher than the prevalence of overweight in a similar population without T1DM. However, the prevalence of obesity is not increased among children and adolescents with T1DM. Recent weigh loss is common at presentation of children with T1DM, including among those who are overweight or obsess.
[4]These frequencies of acanthosis nigricans are based on a registry study in the United States. Populations with lower rates of obesity or difference ethnic mixes may have different results.
[5]Autoantibodies to insulin (IAA), islet cell cytoplasm (ICA), glutamic acid decarboxylase (GAD), tyrosine phosphatase (insulinoma associated) antibody (IA-2 and IA-2β), or zine channel antibody (ZnT8) are present at diagnosis in 85% to 89% of patients with T1DM.
[6]One study reported that 9.8% of youth with phenotypic T2DM have pancreatic antibodies to IA-2 and/or GAD. HLA: Human leukocyte antigen.

reversibility[21]. Some studies demonstrated an increased risk of cardiovascular events among patients who fail to complete exercise stress test regardless of the presence of negative test results[21].

The decisions regarding coronary catheterisation and revascularisation should be considered based on cardiologist recommendations. Patients with significant coronary pathology that is not amenable to revascularisation are not candidates for pancreatic transplantation[20].

SUGGESTED POST-OPERATIVE FOLLOW UP PLAN

Following successful transplantation BTS recommends reviewing the recipients in clinic twice to three times per week for the first month, weekly visits for the next two months, monthly for another three months, then every 2-3 months later on[22]. The clinic visit should include a detailed history of any new symptoms, careful medical examination and appropriate laboratory investigations (including immune-suppressant drug levels if possible). The patient care should involve a multidis-ciplinary team including a pharmacist, social worker, dietician, and psychologist[22].

Meticulous pancreatic donor and recipient selection criteria together with the modern immune suppression protocols have steadily decreased the incidence of pancreatic rejection to range between 10% to 20% in the first year post-transplant[2]. The majority of the early complications of the transplantation can be attributed to surgical and technical failures rather than an immunological injury. Complications include anastomotic leak, vascular thrombosis of the graft, graft pancreatitis, and infection[2,23].
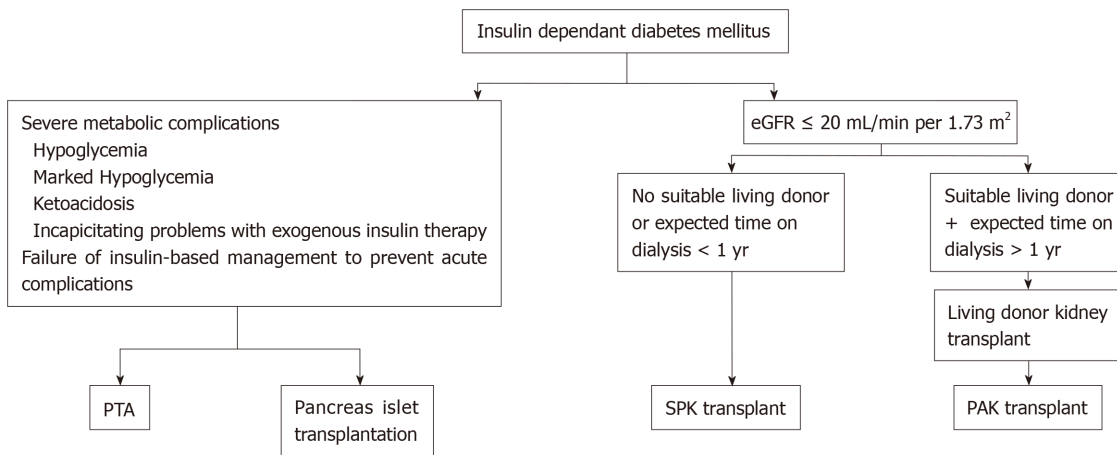
ACUTE REJECTION

Figure 2 Algorithm for clinical decision making for diabetic patients. KTA: Kidney transplant alone; SPK: Simultaneous pancreas-kidney; PAK: Pancreas after kidney; PTA: Pancreas transplant alone.

Most cases of pancreas allograft rejection are asymptomatic, so we should keep a high index of suspicion to detect allograft rejection early enough to allow early initiation of the proper therapy. The islet cells are spared in the initial phase of rejection, and hyperglycaemia is a late finding[2]. We should start our workup once allograft dysfunction is suspected (*e.g.*, elevated serum amylase and/or lipase)[2,24]. A recommended approach for evaluation of pancreatic allograft dysfunction is illustrated in Figure 5[24].

Maintenance immunosuppressive therapy for pancreatic transplantation is similar for that used for kidney transplantation. Most centres use a combination of a calcineurin inhibitor (predominantly tacrolimus), an antimetabolite (mycophenolate mofetil or mycophenolate sodium), and low-dose corticosteroids[2,20]. Induction therapy with lymphocyte-depleting agents (*e.g.*, antithymocyte globulin and alemtuzumab) allows early steroid withdrawal and steroid free regimens which are adopted by some centres[2].

ISLET CELL TRANSPLANTATION

Islet transplantation is an evolving and promising therapeutic option for management of type 1 DM. Successful isolation of islet cells from the whole pancreas is followed by infusion of the cells to the portal vein of the recipient via a percutaneous catheter as illustrated in Figure 6[25].

Keeping in mind that the major mass of the pancreas if formed of exocrine gland with only scattered clusters of endocrine cells, separation of islet cells from exocrine part will not only allow transplantation via minimally invasive technique (infusion of islets isolated from cadaveric pancreas via the portal vein), but it will also avoid vascular and allograft duodenal anastomoses, hence avoiding an essential source of surgical complications[2].

On the other hand, this therapeutic option is facing significant challenges that include: Achieving insulin independence necessitates transplantation of an adequate islet mass, which requires isolation from multiple donors (typically 2 to 4 donors), thus islet cell recipients are exposed to numerous human leukocyte antigen (HLA) mismatches which may jeopardize the possibility of future transplantation due to sensitization and formation of donor-specific antibodies[2,23]; The patient would require lifelong immune suppression even if received islet cell transplantation alone[2,23]; Despite the satisfactory short-term outcome of this technique (about 80% of the cases remained insulin independent after two years), the long-term outcome is still disappointing[2]; In the case of advanced CKD in addition to DM, Islet cell transplantation alone is not a valid option in the management of such medical condition.

CONCLUSION

There is no individual management plan for diabetic patients with advanced CKD; instead, we have different management options that depend on the patient co-morbidities as well as personal preferences. Nevertheless, each option has its

Table 2 Kidney transplant graft failure rates associated with simultaneous pancreas-kidney and pancreas after kidney[8]

Type of the allograft	1 yr	5 yr	10 yr
SPK	3.1%	16.5%	37.7%
PAK (deceased donor)	3.3%	21.2%	51.2%
PAK (living donor)	3.0%	13.7%	37.0%

SPK: Simultaneous pancreas-kidney; PAK: Pancreas after kidney.

limitations and possible complications. The best management plan for diabetic patient approaching ESRD is SPK which will offer the best long-term survival, in addition to the better quality of life and regression of most of DM complications. However, this approach is associated with early increased risk of morbidity and mortality. PTA and islet cell transplantation are possible options for managing diabetic patients. However, they are not suitable alone for patients with concomitant advanced CKD. The pretransplant workup for SPK is more stringent compared to kidney transplantation alone to minimise the risk of early postoperative morbidity and mortality and to achieve long-term patient and graft survival. Islet cell transplantation carries the risk of sensitisation against a group of HLA antigens, which makes the patients less likely to get a compatible kidney allograft in the future. PAK is not recommended above the age of 50 as it is negatively affecting the survival of patients older than 50 years. Additionally, it may result in loss of kidney allograft as a complication of this major intervention.

Table 3 Sample of studies evaluating the effect of pancreatic transplantation on the complications of diabetes mellitus

Ref.	Patient cohorts	Outcomes of interest	Time after transplant (yr)	Results
Cardiovascular disease				
Fiorina *et al*[9], 2000	SPK (*n* = 42) *vs* KTA (*n* = 26) *vs* type 1 diabetes (*n* = 20)	Left ventricular systolic and diastolic function assessed by radionuclideventriculography	4 yr	Left ventricular ejection fraction was higher in SPK recipients than in KTA recipients [75.7 (SD 1.8%) *vs* 65.3% (2.8%); *P* = 0.02] and type 1 diabetes controls (75.7 (1.8%) *vs* 61.2 (3.7%); *P* = 0.004).
Biesenbach *et al*[10], 2005	SPK (*n* = 12) *vs* KTA (*n* = 10)	Composite endpoint of myocardial infarction, stroke, and amputation	10 yr	Lower incidence of myocardial infarction (16% *vs* 50%), stroke (16% *vs* 40%), and amputations (16% *vs* 30%) in SPK *vs* KTA recipients (*P* < 0.05 for composite endpoint of all three events)
Diabetic nephropathy				
Fioretto *et al*[11], 1998	PTA: Pre-transplant *vs* post-transplant (*n* = 8)	Native kidney biopsy:structural morphology before and after transplant	10 yr	Improvement in glomerular basement membrane thickening, tubular basement membrane thickening, and mesangial expansion after transplantation compared with before
Boggi *et al*[12], 2011	PTA: Pre-transplant *vs* post-transplant (*n* = 71)	Proteinuria and estimatedGFR (eGFR)	Up to 4 yr	Overall, proteinuria decreased from 1.36 (SD 2.72) g/d pre-transplant to 0.29 (0.51) g/d post-transplant (*P* < 0.01) eGFR decreased by about 20% from 94 (39) mL/min per 1.73m2 to 75 (22) mL/min per 1.73 m^2 (*P* < 0.01)
Diabetic neuropathy				
Havrdova *et al*[13], 2016	SPK: Pre-transplant *vs* post-transplant (*n* = 12)	Epidermal nerve fiberdensity on skin biopsy, autonomic function tests, and nerve conduction studies	Up to 8 yr	No improvement in epidermal nerve fiber density or functional deficits on autonomic function tests
Boggi *et al*[12], 2011	PTA: Pre-transplant *vs* post-transplant (*n* = 71)	Clinical neurologicexamination (vibration threshold), nerve conduction studies, and autonomic function tests (lying-to-standing test)	Up to 4 yr	Significant improvement in mean vibration thresholds, nerve conduction studies, and autonomic function tests after PTA compared with before
Diabetic retinopathy				
Boggi *et al*[12], 2011	PTA: Pre-transplant *vs* post-transplant (*n* = 71)	Visual acuity scores andfundoscopic examination	Up to 4 yr	Before transplantation, 7.5% of patients had no retinopathy and remained lesion-free at 4 yr. Of the 29.5% with non-proliferative retinopathy, 75% improved and 25% remained unchanged. In the remainder with proliferative retinopathy, lesions remained stable in 82% and progressed in 18%

| Giannarelli *et al*[14], 2006 | PTA (*n* = 33) *vs* type 1 diabetes (*n* = 35) | Visual acuity scores, fundoscopic examination, and angiography in selected cases | Up to 30 mo | Before transplant, 9% of patients with PTA and 6% of those with type1 diabetes had no retinopathy, 24% and 29% had non-proliferative retinopathy, and 67% and 66% had proliferative retinopathy. Overall, the percentage of patients with improved or stabilized retinopathy was significantly higher in the PTA group (*P* < 0.01) |
| Koznarova *et al*[15], 2000 | SPK (*n* = 43) **Vs** KTA (*n* = 45) | Visual acuity scores and fundoscopic examination | 3 yr | In the SPK group, fundoscopic findings at the end of follow-up had improved, stabilized, or deteriorated in 21.3%, 61.7%, and 17.0%, respectively. In the KTA group these figures were 6.1 %, 48.8%, and 45.1% (*P* < 0.001) |

KTA: Kidney transplant alone; SPK: Simultaneous pancreas-kidney; PAK: Pancreas after kidney.

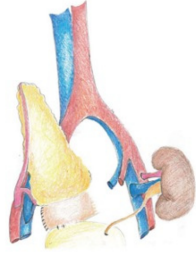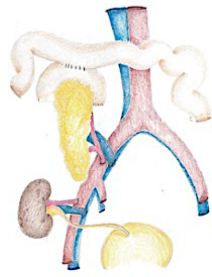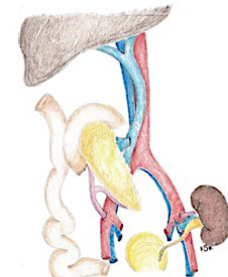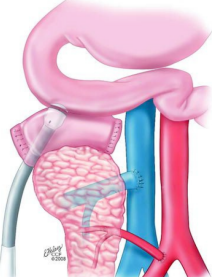| Table 4 Complications of pancreatic transplantation[19]	
Complications	
Early complications	
Allograft parenchymal complications	Acute pancreatitis
	Necrotizing pancreatitis
	Fistulous tracts
Infection and abscesses	
Entric complications	Anastomosis leakage at duodeno-enterostomy
	Ileus Colonic infection.
Vascular complications	Venous or arterial graft thrombosis
	Acute bleeding
Late complications	
Allograft parenchymal complications	Rejection
	Pseudocyst formation
	Post-transplant lymphoproliferative disease
Enteric complications	Small bowel obstruction
	Colonic infection
Vascular complications	Arterial or venous pseudoaneurysms

Procedure	Advantages	Disadvantages
Bladder exocrine drainage and systemic venous endocrine drainage[17]	Pancreatic dysfunction can be detected early by changes of urinary amylase Easley accessible for biopsy Reduced rate of infection due to the relative sterility of the lower urinary tract Technical considerations (Bladder vasculature promote healing, bladder mobilisation permits tension-free, multi-layer anastomosis, Control of anastomotic leakage can be achieved by bladder catheter)	Fluid and electrolyte imbalance Metabolic acidosis Urologic complications (cystitis, haematuria, urethritis, balanitis and urethral stricture) Lower urinary tract infection and stone formation Reflux pancreatitis Enteric conversion if indicated will expose the patient to another major surgery
Enteric exocrine drainage and systemic venous endocrine drainage[17]	More physiologic approach Avoid urologic complications Avoid the future risk of enteric conversion	Higher incidence of pancreatitis, leakage of pancreatic enzymes, and peripancreatic fluid collections More risk of anastomotic leakage, peritonitis, intra-abdominal collection and sepsis Inability to measure exocrine secretions for early detection of graft dysfunction Allograft biopsy is more challenging Occasional need for diverting Roux en y limb
Enteric exocrine drainage and portal venous endocrine drainage[17]	Same advantages mentioned above in addition to: Avoid the risk of postprandial hypoglycaemia Better lipoprotein metabolism	Same points as mentioned above in addition to: Higher risk of vascular thrombosis
Duodenal exocrine drainage and systemic venous endocrine drainage[18]	A modification of enteric exocrine drainage with systemic venous endocrine drainage with additional benefits in the form of: Improved accessibility for biopsy via endoscopy[3,16] It expands the options for exocrine drainage sites, especially in cases of pancreas retransplantation[16]	Same disadvantages mentioned above with enteric exocrine drainage and systemic venous endocrine drainage except for relatively easily accessible allograft

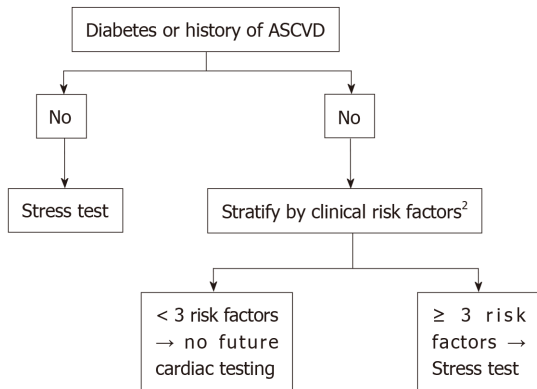**Figure 3 Various pancreatic implantation techniques.**

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All should undergo cardiac testing
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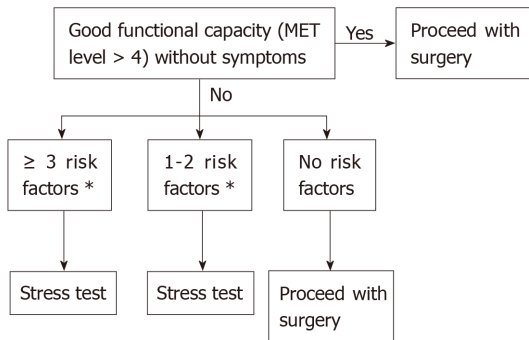
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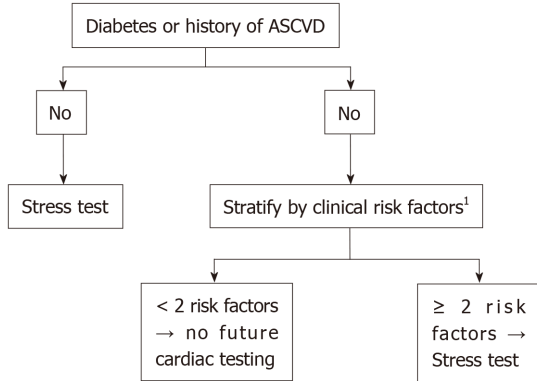
Figure 4 Outlines of preoperative cardiac risk assessment guidelines. [1]Hypertension, age (> 45 for men or > 55 for women), cigarette smoking, left ventricular hypertrophy, dyslipidemia, family history of coronary disease. [2]Hypertension, left ventricular hypertrophy, dyslipidemia, age > 60, > one year on dialysis. [3]Ischemic heart disease, cerebrovascular disease, renal insufficiency, diabetes. KDOQI: Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines; AST: American Society of Transplantation; Lisbon: Report of the Lisbon Conference on the Care of the Kidney Transplant Recipient; ACC/AHA: American College of Cardiology/American Heart Association.
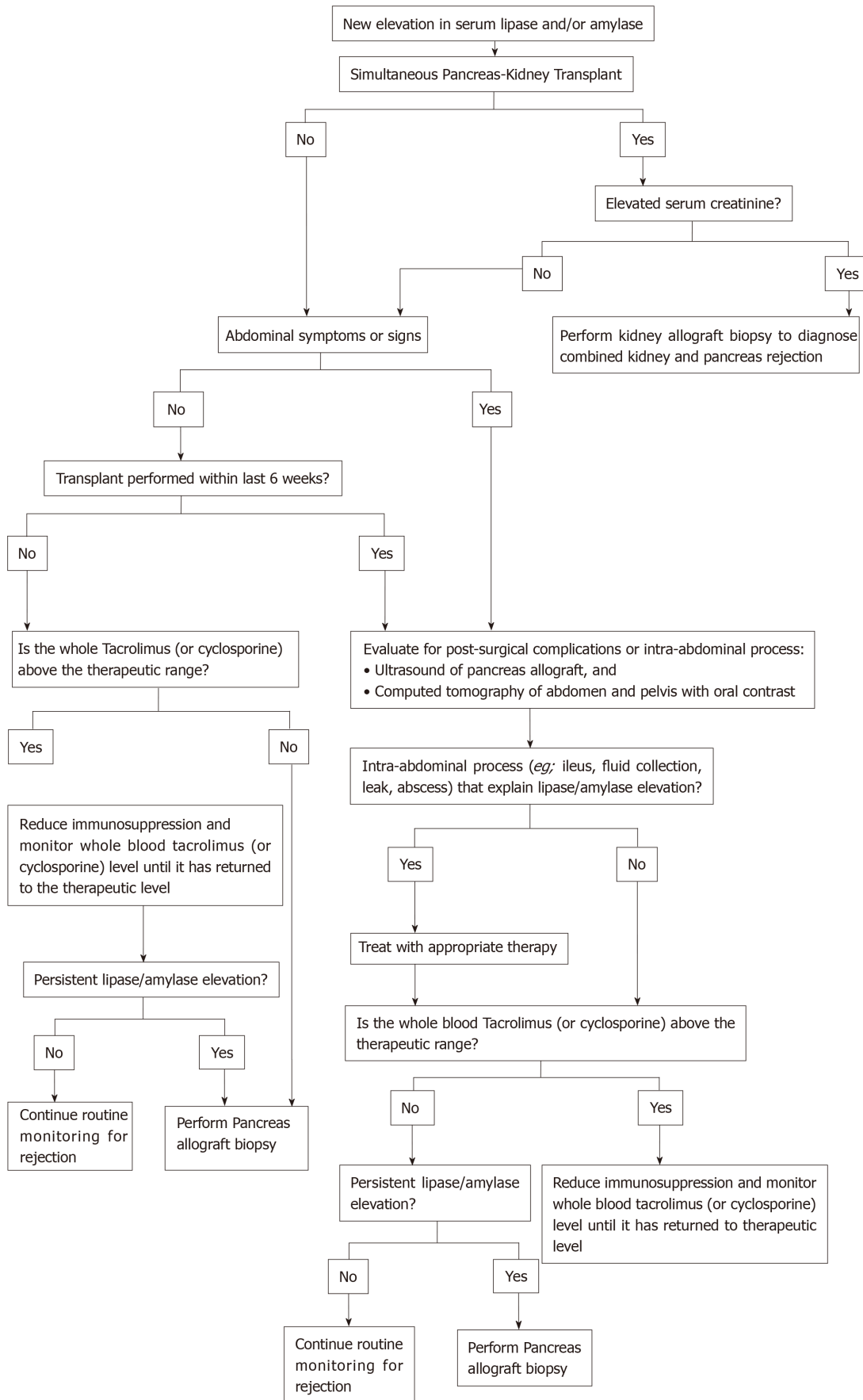
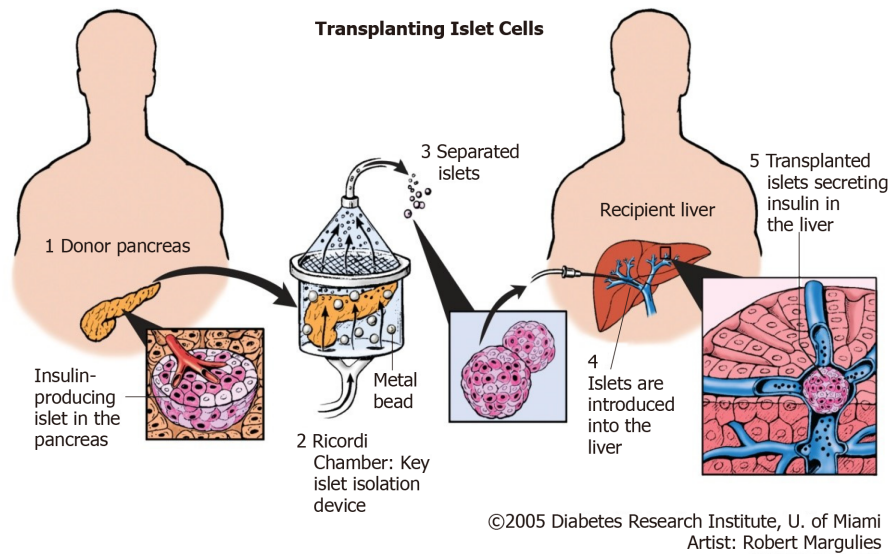**Figure 5 Algorithm for evaluation of pancreatic allograft dysfunction**[24].

Transplanting Islet Cells

Figure 6 **Principles of islet cell transplantation**[25]**.**

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