Transplant options for patients with diabetes and advanced kidney disease: a review

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Transplant Options for Patients With Diabetes and Advanced Kidney Disease: A Review

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Optimal glycemic control in kidney transplant recipients with diabetes is associated with improved morbidity and better patient and allograft survival. Transplant options for patients with diabetes requiring insulin therapy and chronic kidney disease who are suitable candidates for kidney transplantation should include consideration of β-cell replacement therapy: pancreas or islet transplantation. International variation related to national regulatory policies exists in offering one or both options to suitable candidates and is further affected by pancreas/islet allocation policies and transplant waiting list dynamics. The selection of appropriate candidates depends on patient age, coexistent morbidities, the timing of referral to the transplant center (predialysis versus on dialysis) and availability of living kidney donors. Therefore, early referral (estimated glomerular filtration rate < 30 mL/min/1.73 m^2) is of the utmost importance to ensure adequate time for informed decision making and thorough pretransplant evaluation. Obesity, cardiovascular disease, peripheral vascular disease, smoking, and frailty are some of the conditions that need to be addressed before acceptance on the transplant list, and ideally before dialysis becoming imminent. This review offers insights into selection of pancreas/islet transplant candidates by transplant centers and an update on posttransplant outcomes, which may have practice implications for referring nephrologists.

Complete author and article information provided before references.

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Am J Kidney Dis. 78(3):418-428. Published online May 14, 2021.

doi: 10.1053/j.ajkd.2021.02.339

Introduction

Patients with diabetes mellitus and advanced kidney disease require special consideration for possible β-cell replacement at the time of or after kidney transplantation. Two established forms of β-cell replacement therapy are whole pancreas[1] and isolated islet cell[2] transplantation. Either pancreas or islet transplantation may be performed simultaneously with or after kidney transplantation for improving glycemic control, eliminating problematic hypoglycemia, improving quality of life, and/or ameliorating the course of diabetes-related complications including kidney graft damage. This review provides an international perspective to these strategies with consideration for patient selection and anticipated outcomes and proposes an algorithm for identifying individuals appropriate for consideration of β-cell replacement therapy in conjunction with kidney transplantation. Pancreas and islet transplantation in nonuremic patients with type 1 diabetes mellitus (T1DM) complicated by hypoglycemia unawareness was the topic of a prior review.[3]

Pancreas or Islet Transplantation

The last decade has seen a significant decline in the numbers of pancreas transplants performed, especially pancreas after kidney transplantation (PAK) in the United States and Europe.[4–6] The possible reasons include decreased referrals due to technological advances in T1DM therapy, specifically automated insulin-delivery systems, and changing demographics of potential recipients—including older age, higher body mass index (BMI), and more advanced cardiovascular disease (CVD). There is a higher prevalence of donors with obesity, which influences pancreas use due to the increased surgical risks. Ironically, the increasing number of pancreata from high BMI donors may be better suited for islet isolation and transplantation,[7] but this option is not uniformly available around the world.

At present pancreas transplantation provides the best long-term outcomes with regard to insulin independence, metabolic control, and stabilization or improvement of secondary complications. Although both pancreas and islet transplantation may be options for patients with T1DM, only whole organ pancreas transplantation is being performed in selected individuals with insulin-dependent type 2 diabetes (T2DM). Optimal β-cell graft function is defined as near-normal glycemic control (hemoglobin A_{1c} [HbA_{1c}] ≤ 6.5%) without severe hypoglycemia or requirement for insulin or other antihyperglycemic therapy, and with an increase in C-peptide from pretransplantation levels; the absence of clinically significant C-peptide production (<0.6 ng/mL [0.200 pmol/mL] stimulated) may indicate a failed β-cell graft.[8] Additionally, Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) defines pancreas graft failure as pancreas transplant removal, subsequent registration for pancreas or islet transplant, recipient death, or insulin requirements ≥ 0.5 units/kg per day for 90 consecutive days.[9]

Pancreas transplantation is typically performed intraperitoneally with arterial inflow from the right iliac artery and the venous drainage systemically into the inferior vena cava or the portal venous system.[1] The pancreatic exocrine

secretions are drained enterically, and occasionally by bladder drainage (Fig 1). Complications may include graft vascular thrombosis (approximately 5%), reperfusion pancreatitis, hemorrhage, anastomotic leaks, fluid collections, small bowel obstruction, and wound complications; up to 40% may need reoperation.[10] This potential surgical morbidity precludes offering pancreas transplantation to significant numbers of patients with diabetes and advanced kidney disease. Morbidity is greater in older patients and those who have advanced CVD or peripheral vascular disease.[10] Because the pancreas is preferably placed in the right lower abdomen, the kidney is usually placed contralaterally, an important consideration for those receiving a kidney transplant alone (KTA) that may be followed by a PAK in the future.

In contrast, islet transplantation is a relatively low-risk procedure, during which purified islet cells are infused into the portal vein either through a percutaneous transhepatic catheter or a minilaparotomy and then engraft in the liver (Fig 1).[2,11] Complications of islet transplantation are infrequent and include portal branch vein thrombosis in <5% and bleeding in <10% of infusion procedures if the percutaneous route is used.[2] In simultaneous islet-kidney transplantation (SIK), islets are usually transplanted within 72 hours after the kidney graft to allow for the separation of islet infusion from induction with high-dose glucocorticoids and/or T-cell depletion with resulting cytokine release, both potentially detrimental to islet survival.[2]

Limitations to islet transplantation include the need for more than one islet infusion from sequential donors (2 to 3) to achieve an adequate engrafted islet mass for insulin-independence and maintenance of long-term metabolic control. Based on Collaborative Islet Transplant Registry (CITR) data, 71% of all recipients of islet transplantation required 2 or more islet infusions.[12] Important predictors

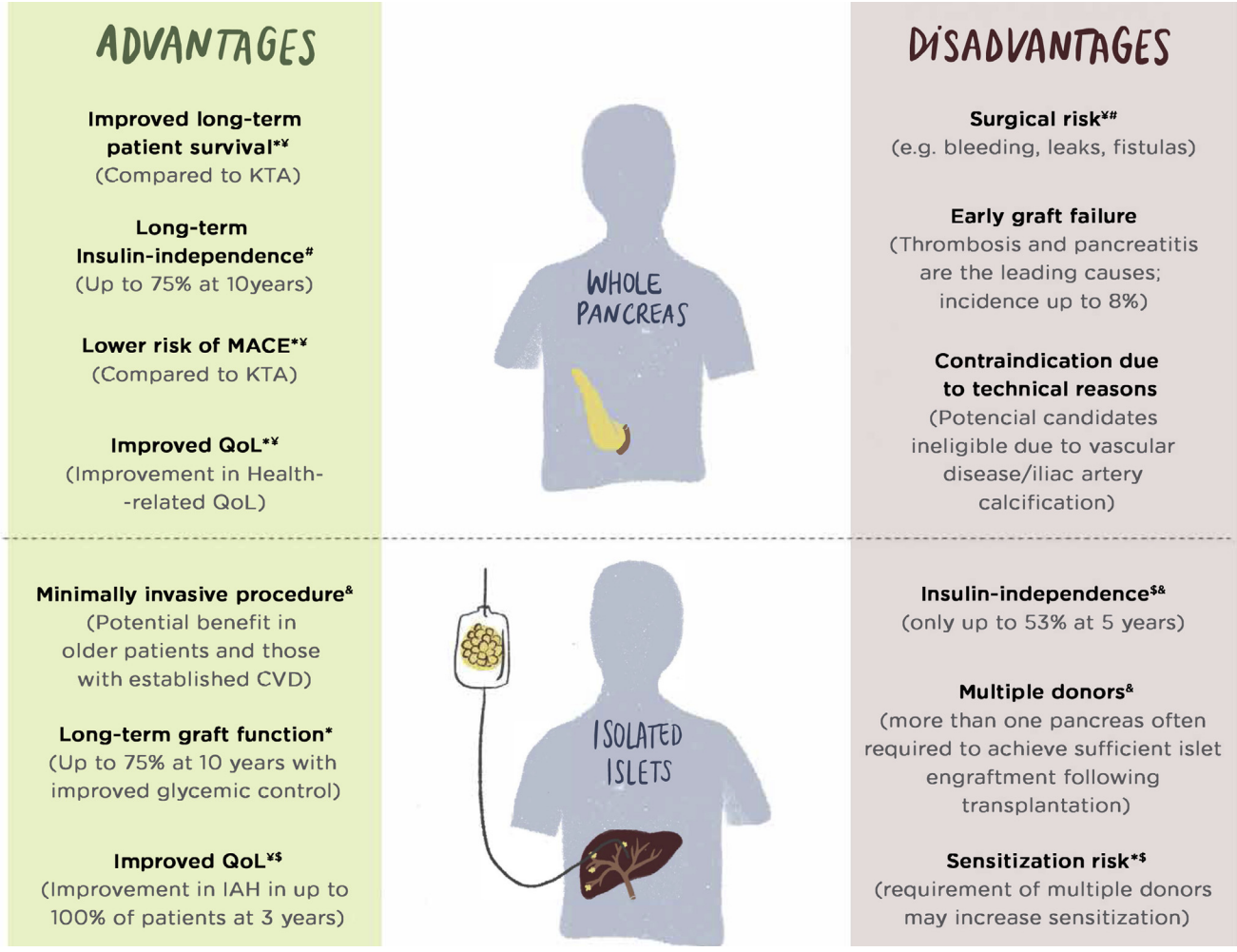

Figure 1. Clinical β-cell replacement treatment alternatives, highlighting major advantages and disadvantages of each procedure. *Data from observational retrospective single-center nonrandomized or registry studies. $Data from randomized clinical trials. ¥Compared with kidney transplant alone. #Compared with islet transplantation. &Compared with pancreas transplantation. Abbreviations: BMI, body mass index; CVD, cardiovascular disease; IAH, impaired awareness of hypoglycemia; KTA, kidney transplant alone; MACE, major adverse cardiovascular events; QoL, quality of life.

of insulin independence after single-donor islet transplantation are pretransplant insulin requirements, peritransplant use of heparin and insulin[13] and the number of infused islets.[14-16] Postinfusion hypoxia and inflammatory response affect islet cell survival before revascularization by the hepatic arterial system. The use of multiple donors may increase the risk for sensitization against human leukocyte antigens. In a phase 3 single cohort study of islet-after-kidney (IAK) transplantation involving 24 participants, the rate of de novo sensitization was up to 22% (5 of 23) over 3 years,[17] which is in fact similar to, and not greater than, that reported in simultaneous pancreas-kidney transplantation (SPK) (21.3%).[18]

Outcomes of pancreas or islets with kidney transplantation in T1DM were compared in a nonrandomized single center retrospective analysis.[19] The 5-year insulin independence rate was higher with SPK/PAK (73.6% vs 9.3% with SIK/IAK), and posttransplant HbA_{1c} levels were lower (7.8%-5.9% vs 8.0%-6.5% with SIK/IAK).[19] Although insulin dosage could only be decreased in <20% of SIK/IAK recipients, there was a significant improvement in HbA_{1c}, and severe hypoglycemic events were significantly reduced to rates similar to those observed with SPK/PAK.[19] Importantly, procedure-related complications were significantly less with islet than pancreas transplantation (relaparotomy rates of 10.5% and 41.5%, respectively), and kidney allograft function shared similar low rates of eGFR decline in both pancreas and islet groups.[19]

Regulations governing cellular product manufacturing currently limit access to islet transplantation to clinical trials in the United States. By contrast, islet transplantation is performed and reimbursed in many other countries such as Australia, Belgium, Canada, the Czech Republic, France, Italy, Japan, the Netherlands, Norway, Poland, Switzerland, Sweden, and the United Kingdom.[20]

Patient Selection and Assessment

In general, pancreas transplantation is considered primarily in younger patients with insulin-dependent diabetes without major cardiovascular or surgical risks who require a kidney transplant, and islet transplantation may be an alternative in older patients with coexisting comorbidities. Carefully selected older recipients, however, may be considered for pancreas transplantation, especially in countries where islet transplantation is not available.[21,22]

Older individuals may increasingly present as transplant candidates as modern approaches to diabetes treatment and more comprehensive management of risk factors including hypertension, hyperlipidemia, and proteinuria have delayed progression to kidney failure in T1DM by at least 10 years compared with previously reported cohorts. Several important factors determine patient selection, including the type of diabetes, degree of reduction in kidney function, degree of glycemic instability and hypoglycemia, disease and treatment burden, magnitude of obesity and insulin requirements, and the presence of comorbidities.

Diabetes Type

Insulin-dependent diabetes resulting from β-cell failure that may be addressed by β-cell replacement is typically T1DM, but may also include selected cases of T2DM and/or other types of diabetes characterized by decreased β-cell secretory capacity including diabetes associated with chronic pancreatitis or pancreatectomy, cystic fibrosis, some genetic forms of diabetes (especially type 3 maturity onset diabetes of the young), mitochondrial cytopathy, and others.[23] Differentiation of T2DM from T1DM is based on the assessment of T1DM-associated autoantibodies (against glutamic acid decarboxylase, islet-associated antigen 2, and zinc transporter 8) and C-peptide level. Although an undetectable or very low level of C-peptide (<0.3 ng/mL [0.1 nmol/L]) is consistent with T1DM, residual C-peptide production may be observed in cases of long-standing T1DM, and the presence of uremia (C-peptide undergoes renal clearance) may allow for detection of higher than expected levels. Usually, in T1DM with advanced kidney disease, C-peptide levels are < 2.0 ng/mL (0.7 nmol/L), so the presence of C-peptide > 2.0 ng/mL (0.7 nmol/L) in the absence of T1DM-associated autoantibodies may be used to confirm T2DM.[24]

There are no uniformly accepted guidelines for pancreas transplantation in patients with T2DM, but in general, patients without significant obesity (BMI < 30-32 kg/m^2) or insulin resistance (insulin requirements of <1 U/kg/d) and low CVD risk are considered.[25] More studies are needed to determine which patients with C-peptide-positive diabetes benefit from pancreas transplantation.

The number of patients with T2DM listed for pancreas transplantation has been steadily growing in the United States, reaching 17.7% for SPK and 10% for PAK.[26] In selected T2DM patients, overall patient and graft survival are similar to T1DM SPK recipients.[27] Surgical and infectious complications and readmissions are similar to those of T1DM recipients, even though BMI is typically higher in T2DM recipients.[28-31] The glycemic control up to 2 years after pancreas transplantation is comparable in recipients with T2DM to that in recipients with T1DM, but more post-transplant weight gain is experienced in T2DM recipients.[30]

Kidney Function

Patients with advanced chronic kidney disease (CKD)—stage 4 and 5 (eGFR 15-30 and < 15 mL/min/1.73 m^2 or on dialysis, respectively) should be evaluated for SPK or SIK as they can accrue waiting time once the eGFR is ≤ 20 mL/min/1.73 m^2. Patients with CKD stage 3 (eGFR between 30 and 60 mL/min/1.73 m^2), who have very labile glycemia and/or debilitating hypoglycemia unawareness and/or rapidly progressive diabetic complications are currently not routinely offered a pancreas or

islet transplant alone (PTA or ITA) due to the risk of accelerated kidney function decline associated with calcineurin inhibitor–based immunosuppression after transplantation.[32,33] Within that group, patients with eGFR > 45-60 mL/min/1.73 m^2 may still benefit from a transplant center evaluation because under exceptional circumstances a PTA or ITA may be considered, granted the risks for kidney function decline requiring imminent dialysis are understood, with plans to follow with a living or deceased donor kidney transplant in that event.

Problematic Hypoglycemia/Hyperglycemia

Problematic hypoglycemia, defined as 2 or more episodes per year of severe hypoglycemia or as one episode associated with impaired awareness of hypoglycemia, extreme glycemic lability, or major fear and maladaptive behavior, is the classic indication for β-cell replacement therapy in patients with preserved kidney function.[8] Patients who have experienced a severe episode of hypoglycemia and also have impaired awareness of hypoglycemia and/or marked glycemic lability are at significantly increased risk for experiencing future severe hypoglycemia and mortality.[34] Problematic hyperglycemia is defined by the presence of recurrent episodes of diabetic ketoacidosis or severe, rapidly progressing secondary complications of diabetes.[8] Problematic hypo- or hyperglycemia is not a prerequisite for kidney transplant candidates to be considered for simultaneous pancreas or islet transplantation but may inform the decision to proceed with β-cell replacement therapy in KTA recipients.[20]

Quality of Life

Quality of life (QoL) may be severely affected in patients with diabetes due to the disease and treatment burden. Studies directly comparing QoL of SPK and KTA recipients are sparse and outdated and therefore may not be applicable to the current era with improved surgical techniques and pancreas allograft survival. Regardless, diabetes-related QoL was shown to be consistently better in SPK versus KTA,[35,36] while general improvement in health was overall better after transplant. Functioning pancreas allograft was found to be an important prerequisite for improved QoL.[37] More recent studies compared QoL before and after SPK and confirmed an improvement after transplant.[38-41] Improved metabolic control was also associated with better health-related and diabetes-related QoL in both islet transplant alone and islet-after-kidney transplantation.[17,42]

More studies are needed in the current era of modern insulin-delivery technology to compare patient-reported outcomes in pancreas versus islet transplant recipients transplanted simultaneously with or after the kidney, as well as KTA using standardized and validated surveys.

Obesity

Increasing BMI in transplant candidates reflects the obesity trends in the general population as well as patients with T1DM,[43] with approximately 20% of wait-listed pancreas transplant candidates having a BMI ≥ 30 kg/m^2.[26,44] Obesity is associated with a higher risk of early graft loss due to graft thrombosis and technical failure as well as compromised long-term pancreas allograft survival and increased risk of mortality.[45] Weight loss may improve transplant eligibility in candidates with both T1DM and T2DM and maximize the benefit-risk ratio of pancreas transplantation. Bariatric surgery could be considered in individuals unable to lose weight with diet and exercise before transplant listing.[46] Sleeve gastrectomy is preferred over Roux-en-Y gastric bypass due to the lower risk of kidney allograft complications, no significant effect on the absorption of immunosuppression, and less risk of alimentary hypoglycemia, which may be exacerbated after pancreas transplantation.[47,48]

Vascular Disease

CVD and peripheral vascular disease are common in patients with diabetes and advanced kidney disease. Additional risk factors include dyslipidemia and smoking,[49] as well as abnormal calcium and phosphate homeostasis, oxidative stress, and inflammation present in patients with kidney failure and associated vascular calcification.[50] The presence of arterial calcification increases the intraoperative technical difficulty for revascularization and correlates closely with CVD events, mortality, and graft loss in pancreas (and kidney) transplant recipients.[51] Thorough CVD disease workup before transplantation is required to mitigate unexpected postoperative cardiovascular events, but local policies vary.

Frailty

Frailty is a well-recognized risk factor leading to adverse outcomes in patients on dialysis. Frailty is also associated with poor outcomes after kidney transplantation, including impaired physical and cognitive functioning, and higher mortality. Transplant centers use various tools to assess for frailty prior to acceptance for transplantation.[52] Frail patients are less likely to be considered for SPK due to the longer postoperative recovery and higher risk of complications. Research is urgently needed to identify interventions that could improve physical and cognitive functioning among frail patients. Whether patients with frailty benefit from islet, rather than pancreas, transplantation when receiving a kidney transplant remains to be determined. Poor vision and severe, frequently debilitating diabetic polyneuropathy, including autonomic instability, are often present in patients with long-standing diabetes and add to the complexity of perioperative and posttransplant care.

Transplant Options

Patients with insulin-dependent diabetes and advanced kidney disease should preferably be referred for evaluation for a β-cell transplant when eGFR is below 30 mL/min/1.73 m^2,

especially in those with rapid kidney function decline (defined as GFR loss > 5 mL/min/1.73 m^2 per year) (Fig 2). Early referral is advised to ensure adequate time for informed decision making and thorough pretransplant evaluation, allowing for early identification and management of any mental and physical health–related barriers to transplantation. Early referrals can facilitate preemptive transplantation and thus avoid debilitating dialysis-related comorbidities and increased mortality and improve patient and graft survival.[53,54]

Recipients With Living Kidney Donors

Successful kidney transplantation is a major determinant of improved survival in kidney and pancreas transplant recipients, mainly due to the reduction of CVD mortality, compared with remaining on dialysis.[55,56] Gruessner et al.[56] demonstrated 4-year patient survival of 81.7% in KTA recipients waiting for pancreas transplant, compared with 58.7% in patients waitlisted for SPK. Hence, patients on or close to dialysis who have a suitable living donor may benefit from proceeding with KTA instead of waiting for SPK. Kidney donors and recipients who are blood type incompatible, cross-match positive, or with high donor-specific antibody profiles may be transplanted through paired exchange programs, which are being increasingly used worldwide.[57]

KTA has a short-term advantage over SPK transplants in terms of lower surgical morbidity and mortality.[55,58-60] In the long term, SPK recipients have been shown to accrue a survival benefit compared with living or deceased donor KTA recipients,[59-62] with a reduction up to 37% of CVD-related mortality (hazard ratio, 0.63 [95% CI, 0.40-0.99]).[62] However in the absence of randomized controlled trials, these outcomes have to be interpreted cautiously due to potential selection bias where healthier patients receive a SPK as well as a shorter dialysis duration due to donor allocation policies.[59,62]

Simultaneous Pancreas-Kidney Transplant and Simultaneous Islet-Kidney Transplant

SPK transplant offers the benefits of a single surgical procedure and induction immunosuppression with superior pancreas allograft outcomes compared with PAK transplant.[63-65] In some countries the pancreas is often allocated with a better quality kidney allograft due to stricter pancreas acceptance criteria and typically with a shorter waiting time compared with a deceased donor KTA.[66] Improvement in surgical techniques and immunosuppression have greatly prolonged pancreas allograft survival,[67] particularly with the use of T-cell depleting antibodies as induction therapy.[55,68-70] The survival benefit in SPK is observed as early as 170 days after

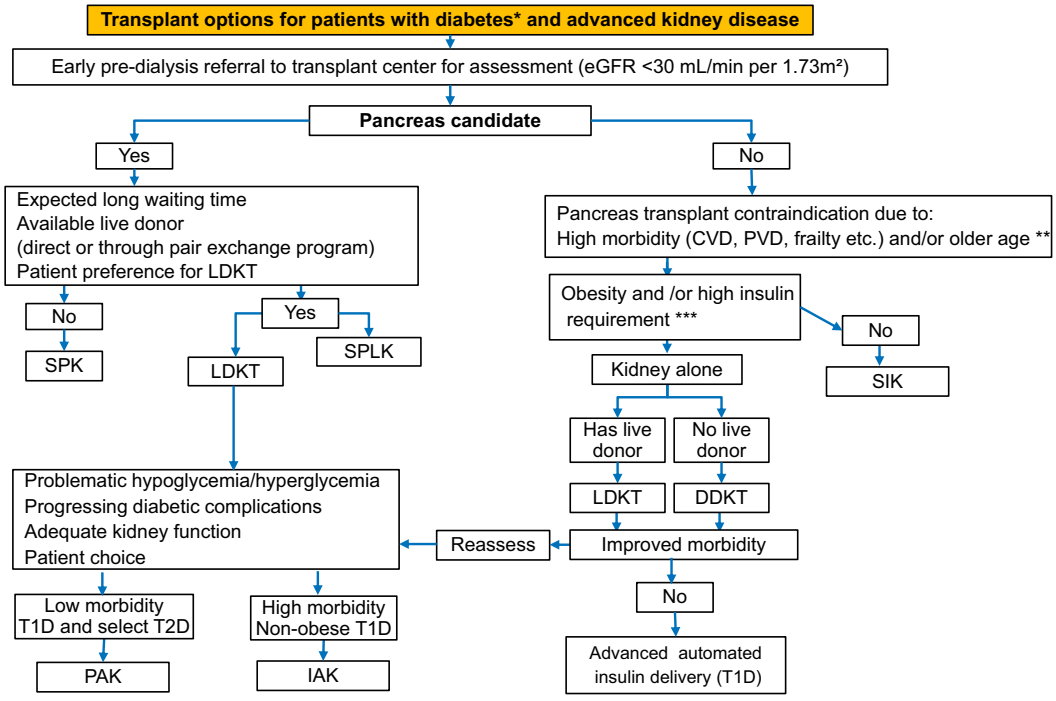

Figure 2. Practical decision-making algorithm for β-cell replacement in patients with insulin-dependent diabetes and advanced kidney disease. Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DDKT, deceased donor kidney transplant; eGFR, estimated glomerular filtration rate; IAK, islet-after-kidney; LDKT, living donor kidney transplant; PAK, pancreas-after-kidney; PVD, peripheral vascular disease; SIK, simultaneous islet-kidney; SPK, simultaneous pancreas-kidney; SPLK, simultaneous deceased donor pancreas with living donor kidney; T1D, type 1 diabetes mellitus; T2D, type 2 diabetes mellitus. *Mainly for patients with type 1 diabetes mellitus; the BMI criteria may vary between the centers; consider patients with T2D with BMI < 30-32 kg/m^2 or after bariatric surgery if insulin dependent. **Center-specific age criteria for pancreas transplantation apply. ***More than 1 unit/kg per day.

transplantation compared with remaining on the wait list.[71]

SPK recipients have long-term survival benefits over KTA, which may be explained by a long-term reduced risk of CVD events[62] and increased kidney allograft survival at 10 years.[61] Pancreas allograft survival in SPK recipients at 1 year and 10 years is 89% and 75%, respectively,[61,67,72] and at 25 years is up to 13%.[73] In addition, insulin-dependent KTA recipients have inferior kidney allograft survival at 10 years (50% vs 61% for SPK or 66% for PAK)[61] and are at increased risk of recurrent diabetic nephropathy,[74,75] demonstrated histologically by the presence of mesangial matrix expansion in up to 64.9% of patients at 5 years after transplant (compared with 27.1% in nondiabetic and 27.7% in patients with non–insulin-dependent diabetes).[74-76]

Simultaneous deceased donor pancreas with living donor kidney (SPLK) transplant is a potential alternative to a SPK when the waiting time for a deceased donor is prolonged and a living kidney donor is available.[77,78] SPLK transplantation has universal and patient-specific benefits, including expanding the pool of available kidneys and potential shorter waiting time for a deceased donor pancreas transplant alone.[77,78] However, the logistics of coordinating a living donor kidney operation with the simultaneous implant in the recipient of a deceased donor pancreas limits wider acceptance in countries where the waiting times for SPK are relatively short.[79] Less commonly, SIK may be offered from a deceased donor, particularly for recipients with T1DM awaiting a deceased donor kidney transplant who are not candidates for or willing to accept the risks of pancreas transplantation.[20]

Pancreas-After-Kidney and Islet-After-Kidney

For patients with T1DM who have undergone successful KTA from either a living or deceased donor, a subsequent PAK or IAK transplant may be an option. PAK may also be considered for selected individuals with insulin-dependent T2DM.[20] PAK is usually performed in recipients who have difficulty with achieving target glycemic control and/or management of diabetes-related complications, and who are willing to accept the potential morbidity of additional surgery. Adequate kidney allograft function, ideally eGFR of at least 40-45 mL/min/1.73 m^2, is needed to buffer the impact of potential perioperative pancreas transplant complications and intensified immunosuppression on long-term kidney allograft function.[80]

PAK has been reported to improve kidney graft survival at 10 years when compared with KTA (66% vs 50%),[61] but these results may be biased by retrospective analysis, patient selection, and lack of a standardized insulin therapy approach in KTA recipients. As for the pancreas allograft, survival has been reported to be inferior in PAK recipients compared with SPK (at 10 years 45% vs 58%, respectively),[61,63] although center variations may exist, with some reporting similar allograft survival between both techniques.[81] Biopsying the kidney as a surrogate marker of pancreas graft rejection in SPK has been considered a key reason for these differences in graft survival,[4] though in concurrent graft biopsies in SPK only 40% of patients presented simultaneous rejection, with 34% and 27% showing discordant kidney and pancreas rejection.[82]

IAK is an alternative β-cell replacement strategy for patients with T1DM and a functioning kidney transplant—including those with early technical pancreas allograft failure after an SPK or PAK. Although insulin independence may be inferior with islet compared with pancreas transplantation (28% at 10 years, vs 45% in PAK),[61,83] insulin independence is observed in 38% to 62% at 1 year,[17,84] and islet graft survival up to 78% at 10 years.[83] IAK is associated with a significant improvement in HbA_{1c} to ≤ 6.0% at 1 year,[17,83] which is maintained at 6.3% at 3 years[17] and 6.7% at 10 years,[83] and further restores awareness of hypoglycemia with a significant improvement in QoL.[17]

Although it was limited to a 6-month follow-up period, the TRIMECO study randomized participants to ITA or IAK versus intensive insulin therapy and confirmed that HbA_{1c} was significantly lower in those who received an islet transplant (5.6% vs 8.2%), with 23 out of 25 patients becoming protected from severe hypoglycemic events compared with only 8 out of the 22 patients receiving optimized medical management. Importantly, a significant improvement in health-related QoL was also confirmed in the transplant group compared with the insulin group.[85]

After islet transplantation, kidney allograft function remains stable,[17,83] without evidence of sensitization against the transplanted kidney despite multiple islet infusions. Longer and larger studies are required to define the impact of islet transplant–associated sensitization on long-term kidney allograft outcomes and retransplantation. Whether KTA recipients with acceptable glucose control and absence of hypoglycemia unawareness benefit from PAK/IAK over state-of-the-art individualized intensive insulin therapy in terms of overall survival and the prevention of progression of micro- and macrovascular complications remains to be determined.

Level of Evidence

The algorithm proposed here is based primarily on retrospective cohort studies and registry analysis data. Studies of IAK have been conducted prospectively,[17,83,84] including under phase 3 registration with the US Food and Drug Administration.[17] One randomized clinical trial comparing ITA and IAK to intensive insulin therapy has been carried out to date.[86] Table 1 summarizes the most relevant studies and outcomes for each treatment alternative. Further studies are required to evaluate differences among treatment alternatives (Box 1).

Conclusions

For patients with insulin-dependent diabetes and advanced kidney disease requiring kidney

Table 1. Retrospective Studies of Outcomes Among Transplant Options for Patients With Insulin-Dependent Diabetes and Advanced Kidney Disease

Study	Population	Design	FU Period	Time on Wait List and/or Dialysis	Patient Survival	Graft Survival	
						Pancreas/ Islet	Kidney
SPK vs KTA							
Lindahl (2016)[62]	SPK (n = 256) vs LDKT (n = 230)	Single center	7.9 y	Wait list: ND Dialysis: SPK: 0.9 y, LDKT: 0.6 y	Survival on FU: 61% for SPK vs 44% for LDKT HR for mortality,[a] SPK vs LDKT CVD related: 0.63 (0.4-0.99); $P = 0.047$ All-cause: 0.81 (0.57-1.16); $P = 0.25$ CAD related: 0.63 (0.36-1.12); $P = 0.12$	—	—
Sollinger (2009)[55]	SPK (n = 1,000) vs LDKT (n = 403) vs DDKT (n = 697)	Single center	20 y	ND	At 10 y: 80% for SPK; 50%-60% for LDKT; 40%-50% for DDKT	—	At 10 y: 38% for SPK; ND for LDKT, DDKT
Barlow (2017)[60]	SPK (n = 1,739) vs LDKT (n = 370)	Registry analysis	13 y	Wait list: SPK, 0.87 y; LDKT, 0.90 y Dialysis: ND	Better in SPK (with functioning pancreas at 90 d) vs LDKT ($P = 0.042$)	—	DGF: 15.5% for SPK vs 7.3% for LDKT ($P < 0.001$) Graft survival at 10 y: 77% for SPK vs 80% for LDKT ($P = 0.25$)
Fridell (2018)[61]	SPK (n = 19,725) vs PAK (n = 5636)	Registry analysis	10 y	Wait list: SPK, 1.2 y; KTA, ND	At 10 y: 70.3% for SPK; 86.3% for KTA[b]	—	69.8% for PALK vs 61.0% for LDKT; 66.0% for PADK vs 50.4% for DDKT
SPK vs PAK							
Fridell (2018)[61]	SPK (n = 19,725) vs PAK (n = 5,636)	Registry analysis	10 y	Wait list: SPK, 1.2 y; PAK, 1.3 y Dialysis: ND	70.3% for SPK vs 63.2% for PAK ($P < 0.001$)	58.7% for SPK vs 44.4% for PALK vs 41.7% for PADK ($P < 0.001$)	61% for SPK vs 69.8% for PALK vs 66.0% for PADK ($P < 0.001$)
Ventura-Aguiar (2018)[63]	SPK (n = 139) vs PALK (n = 18) vs PADK (n = 28)	Single center	10 y	Wait list: SPK, 1.6 y; PALK, 0.5 y; PADK, 0.3 y Dialysis: SPK, 2.9 y; PALK, 1.0 y; PADK, 2.8 y	$P > 0.05$ for SPK vs PALK vs PADK	PALK & PADK inferior to SPK ($P < 0.05$)	$P > 0.05$ for SPK vs PALK vs PADK
Parajuli (2019)[81]	SPK (n = 611) vs PALK (n = 12) vs PADK (n = 12)	Single center	15 y	Wait list: SPK, 0.5 y; PAK, 1.2 y Dialysis: ND	68% for SPK vs 71% for PAK ($P = 0.79$)	62% for SPK vs 71% for PAK ($P = 0.38$); $P = 0.68$ for SPK vs PALK vs PADK	66% for SPK vs 50% for PAK ($P = 0.11$); $P = 0.59$ for SPK vs PALK vs PADK
SIK/IAK vs SPK/PAK							
Frank (2004)[86]	IAK (n = 4) vs SPK/PAK (n = 30)	Single center	IAK: 1.4 y; SPK/PAK: 1.2 y	ND	At FU: 96.6% for SPK/PAK vs 100% for IAK	Graft function (as per C-peptide secretion): no difference Insulin independence: superior for SPK/PAK ($P < .04$)	ND
Lehmann (2015)[19]	SPK/PAK (n = 94) vs SIK/IAK (n = 38)	Single center	SPK/PAK: 5.6 y; SIK/IAK: 6.4 y	Wait list: SPK/PAK, 0.9 y SIK/IAK, 1.4 y	At 10 y: 88.5% for SPK/PAK vs 65.4% for SIK/IAK	Insulin independence at 5 y: 73.6% for SPK/PAK vs 9.3% for SIK/IAK	ΔeGFR at 13 y: −9.5 ± 23 for SPK/PAK vs −13.3 ± 13.8 for SIK/IAK

Abbreviations: CAD, coronary artery disease; DDKT, deceased donor kidney transplant; DGF, delayed graft function; ΔeGFR, change in estimated glomerular filtration rate (in mL/min); FU, follow-up; IAK, islet-after-kidney; ITA, islet transplant alone; KTA, kidney transplant alone; ND, no data (was not mentioned in report); PADK, pancreas-after-deceased-donor-kidney; PAK, pancreas-after-kidney; PALK, pancreas-after-living-donor-kidney; PTA, pancreas transplant alone; SIK, simultaneous islet-kidney; SPK, simultaneous pancreas-kidney.

[a]Values in parentheses are 95% confidence intervals.

[b]For only those awaiting a PAK.

Box 1. Issues for Future Research

- Benefits of early (eGFR > 20 mL/min/1.73 m^2) SPK transplant in patients with impaired kidney function and rapidly progressive diabetic complications and/or problematic hypo- or hyperglycemia despite advanced automated insulin-delivery system.
- Patient survival and micro- and macrovascular diabetes complications in PAK recipients as compared with KTA on advanced automated insulin-delivery systems.
- Kidney allograft survival in PAK recipients as compared with KTA on advanced automated insulin-delivery systems.
- Outcomes of pancreas versus islet transplantation in patients with C-peptide–positive diabetes; appropriate selection of candidates for degrees of insulin resistance.
- Assessment of pancreas insulin secretory reserve in patients with type 2 diabetes and advanced chronic kidney disease.
- Preservation of kidney function in PTA/ITA recipients with diabetic kidney disease.
- Surgical pancreas transplant–related morbidity and long-term outcomes in high-risk recipients (eg, age > 55 years, frailty or significant physical impairment, advanced cardiovascular and peripheral vascular disease).
- Pancreas allograft outcomes in SPK recipients as compared with the solitary pancreas transplant in terms of alloimmune rejection, autoimmune recurrence, and graft survival.
- Long-term risk of sensitization with islet transplantation in IAK recipients.
- The impact of cytomegalovirus disease and its prevention on pancreas and islet transplant outcomes.
- Organ donor allocation for pancreas versus islet transplantation.
- Randomized studies evaluating efficacy of less nephrotoxic and diabetogenic immunosuppression.
- The impact of recipient prehabilitation strategies on long-term outcomes.
- Organ preservation strategies to reduce ischemia reperfusion injury and optimize isolated islet yields and function.
- Comparison of patient-reported outcomes between SPK, SIK, and KTA recipients, as well as between PAK, IAK, and KTA recipients.

Abbreviations: eGFR, estimated glomerular filtration rate; IAK, islet after kidney; ITA, islet transplant alone; KTA, kidney transplant alone; PAK, pancreas after kidney; PTA, pancreas transplant alone; SPK, simultaneous pancreas-kidney.

transplantation, β-cell replacement should be considered to provide a complete spectrum of cure for β-cell deficiency. Advances in β-cell replacement allow individualized therapy options depending on patient priority, coexistent morbidity, and the availability of a living kidney donor. Ideally, both pancreas and islet transplantation should be offered according to medical condition and patient preference[20] rather than dictated by regional availability for a particular patient with diabetes and advanced kidney disease.

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Support: Prof Saudek was supported by a research grant from the Ministry of Education Youth and Sports of the Czech Republic No. LTAUSA19073. Prof Vantyghem was supported by the French Ministry of Health, PHRC (Programme hospitalier de recherche clinique) 2001, the European Community (Fond Européen de Développement Régional), Conseil Régional du Nord-Pas-de-Calais (IFR 114, Institut de Médecine Prédictive et de Recherche Thérapeutique), Programme d'investissements d'avenir Labex European Genomic Institute for Diabetes ANR-10-LABX-46). Prof Ventura-Aguiar was supported by a research grant from the Spanish Ministry of Science and Innovation (grant PI16-00167 of Instituto Salud Carlos III); Prof Rickels was supported by Public Health Services Research Grant R01 DK091331 and the Institute for Diabetes, Obesity & Metabolism at the University of Pennsylvania Perelman School of Medicine. The funders had no role in defining the content of the article.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Acknowledgements: The authors thank the Council of the International Pancreas & Islet Transplant Association, a section of the Transplantation Society, for providing advice during concept development and the formation of the writing committee, and Aristea Slikas of the University of Pennsylvania Institute for Diabetes, Obesity & Metabolism for providing editorial assistance.

Peer Review: Received November 15, 2020. Evaluated by 3 external peer reviewers, with direct editorial input from an Associate Editor, who served as Acting Editor-in-Chief. Accepted in revised form February 15, 2021. The involvement of an Acting Editor-in-Chief was to comply with AJKD's procedures for

potential conflicts of interest for editors, described in the Information for Authors & Journal Policies.

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