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Expansion of the Pancreas Transplant Recipient Pool: Appropriate for Most or Are There Limits?

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Abstract

Purpose of review Pancreas transplantation is currently the only available therapy capable of reliably reestablishing normal glucose homeostasis independent of exogenous insulin in patients with diabetes. Historically, this procedure was reserved exclusively for suitable candidates with Type 1 diabetes mellitus (T1DM).

Recent findings Indications for pancreas transplantation have been liberalized to include patients with T1DM that were previously not considered suitable, select candidates with Type 2 DM, and rarely for less common forms of diabetes.

Summary This review examines standard indications and contraindications for pancreas transplantation including expansion of criteria for candidates who are older, have obesity, or are medically or surgically complex. It remains unclear whether pancreas transplant is appropriate for most candidates with diabetes, particularly those with uremia, irrespective of age, size, diabetes type, or insulin need/dose, or if it remains appropriate only for a select group of patients.

Keywords Pancreas Transplantation · Recipient Selection · Diabetes Mellitus Type 1 · Diabetes Mellitus Type 2

Abbreviations

BMI	Body Mass Index
CFRD	Cystic fibrosis related diabetes
CrCl	Creatinine clearance
GFR	Glomerular filtration rate
OPTN	Organ Procurement and Transplantation Network
PAK	Pancreas after kidney
PTA	Pancreas transplant alone
SPK	Simultaneous pancreas and kidney
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
US	United States

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Introduction

Whole organ pancreas transplantation is currently the only available therapy capable of reliably reestablishing normal glucose homeostasis independent of exogenous insulin (or other medications) in patients with diabetes and may prevent, stabilize, or even reverse progressive diabetic complications [1–5]. Historically, this procedure was reserved exclusively for suitable candidates with insulin-requiring Type 1 diabetes mellitus (T1DM) and acceptable surgical risks in terms of age, body habitus, and associated comorbidities. In recent years, indications for pancreas transplantation have been liberalized to include patients with T1DM that were previously not considered to be candidates, select candidates with Type 2 diabetes mellitus (T2DM), and rarely for patients with other less common forms of diabetes. In this review, we will examine the standard indications and contraindications for pancreas transplantation including expansion of criteria to consider candidates who are older, have obesity, or are medically or surgically complex.

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Standard Indications for Pancreas Transplantation

Since the introduction of clinical pancreas transplantation by Lillehei and Kelly at the University of Minnesota nearly sixty years ago [6], outcomes have consistently improved secondary to advances in donor identification and management, organ procurement and preservation, immunosuppression, operative technique, anti-infective prophylaxis, and perioperative management [7–10]. The vast majority of pancreas transplants have been performed in appropriately selected patients with type 1 diabetes mellitus (T1DM) and advanced kidney disease as a simultaneous pancreas-kidney (SPK) transplant. When weighing the risk–benefit balance of pancreas transplantation, in addition to the surgical risks, patients would be trading lifelong reliance on insulin therapy and the long-term complications of diabetes (vision loss, microvascular and macrovascular disease, peripheral and autonomic neuropathy, renal failure, and impairment in quality and quantity of life) for chronic immunosuppression with the potential for specific drug toxicities as well as risks for opportunistic infections and malignancies. Historically, the ideal subset of patients with diabetes that were considered appropriate for pancreas transplantation included those with insulin-treated diabetes under consideration for kidney transplantation for end stage renal disease, usually secondary to diabetic nephropathy. These patients would already be committed to the need for chronic immunosuppression for the kidney transplant, thus effectively eliminating the concern for additional risks of immunosuppression for the pancreas allograft. In this setting, candidates would be offered a kidney and pancreas transplant that could either be performed simultaneously (SPK transplant) or sequentially, particularly in the setting of a living donor kidney transplant followed by a deceased donor pancreas transplant (pancreas after kidney [PAK] transplant). Both approaches offer the patient with diabetes and uremia a kidney and pancreas transplant that achieve similar improved long-term patient survival and quality of life compared to remaining on dialysis with diabetes [11, 12]. In fact, one of the greatest opportunities for pancreas transplant programmatic growth is to identify prior kidney transplant recipients who, at the time of renal transplant, either did not meet institutional pancreas transplant listing criteria or opted for kidney transplantation alone but now meet modern criteria for a PAK transplant [13]. Both SPK and sequential PAK transplants became Medicare-approved procedures in July 1999. Additionally, highly selected candidates with potentially life-threatening metabolic complications from hyperlabile diabetes such as hypoglycemia unawareness, recurrent episodes of ketoacidosis, or progressive nonrenal complications in the setting of acceptable renal function may benefit from pancreas transplant alone [PTA] in the absence of a kidney transplant. PTA became a Medicare-approved procedure in 2006. Rarely, insulin allergy, extreme insulin sensitivity, or erratic insulin absorption may result in true failures of exogenous insulin therapy irrespective of compliance and these patients may likewise benefit from PTA [14].

In order to accrue waiting time for an SPK transplant in the United States (US), a candidate must:

- Be registered with the Organ Procurement and Transplantation Network (OPTN) for an SPK transplant.
- Be diagnosed with diabetes (although having pancreatic exocrine insufficiency or requiring the procurement or transplantation of a pancreas as part of a multivisceral transplant for technical reasons are also included as indications for registering for a pancreas transplant).
- Qualify for kidney waiting time according to OPTN kidney allocation policy (although patients can be listed for SPK transplant without accruing waiting time).
- Be on insulin therapy [15].

Initially, following the launch of the "new" pancreas allocation policy in October 2014, there were additional qualifying criteria regarding serum C-peptide levels and body mass index (BMI) limitations, which have since been eliminated. Currently, OPTN policy for accruing waiting time on the kidney list, and therefore the SPK transplant list, specifies that waiting time dates to the earliest of the following criteria:

- The candidate's registration date with a glomerular filtration rate (GFR) or measured or estimated creatinine clearance (CrCl) less than or equal to 20 mL/min/1.73 m^2. Of note, the OPTN recently mandated that exclusively race-neutral estimated GFR calculations be applied for this listing criterion.
- The date after registration that a candidate's GFR or measured or estimated CrCl becomes less than or equal to 20 mL/min/1.73m^2.
- For Black patients, waiting time accrual can be backdated to a qualifying eGFR or CrCl that was over 20 mL/min/1.73 m^2 and would have been 20 mL/min/1.73 m^2 or less if a race-neutral calculation had been used regardless of when the patient is registered on the waiting list.
- The date that the candidate began receiving dialysis regardless of when the patient is registered on the waiting list [16].

For this reason, if a candidate is either considering or thought to be a potential candidate for a sequential PAK transplant following either a living or deceased donor renal transplant, it is still prudent to list them for an SPK transplant to appropriately initiate their waiting time for both organs, and then transfer that time to the PAK list following the kidney transplant. For PTA, the candidate must only meet registration criteria and the waiting time begins at listing irrespective of renal function [17]. Note that all criteria for pancreas registration and waiting time accrual only stipulate insulin-requiring diabetes without specifying type or mechanism of diabetes, age, body size, burden of vascular disease, or other anticipated medical or surgical complexities. Consequently, each center can exercise discretion and only list candidates within their capabilities, limitations, and comfort level. Given that nearly 50% of pancreas transplant centers in the US perform 5 or less pancreas transplants per year, and only 25% of centers perform any solitary pancreas transplants each year, it is not surprising that the potential for huge variations in listing practices exist amongst programs and many patients may be underserved or never even considered for pancreas transplantation.

Contraindications to pancreas transplantation mirror those for most other solid organ transplants [18, 19]. Absolute contraindications include active or untreated malignancy and active or chronic infections. However, even in these circumstances the candidates must be considered on a case-by-case basis as to the type, extent, and stage of disease. Ultimately, the prognosis and successful treatment of cancer or infection and anticipated recurrence-free survival must be balanced against the projected survival of a patient with diabetes on dialysis or with other progressive diabetic complications. The most important aspects of the candidate's evaluation and listing process are the overall assessment of cardiovascular and pulmonary risk, burden, and reserve because untreatable or irremediable cardiac or pulmonary disease precluding major surgery is an absolute contraindication to transplant. Many centers would also consider noncompliance, lack of adequate social support or resources, and active illicit drug abuse in this category, although many centers are currently accepting candidates that consume marijuana/cannabis, particularly when used for medical indications and also in States where it is not illegal. However, it is not yet entirely clear if this may impact long-term allograft survival, particularly in cases of dependence or abuse [19–24]. Tobacco and alcohol abuse also are included in this category, particularly if the candidate has either apparent smoking- or alcohol-related morbidities or if the patient has not been abstinent for a variable period of time. However, it is important to note that although smoking or alcohol cessation are strongly encouraged, tobacco or alcohol use (as opposed to abuse) are not by themselves absolute contraindications to pancreas transplantation.

Beyond these absolute contraindications, there are several relative contraindications including advanced age, elevated BMI, prior surgery/retransplantation, and advanced atherosclerotic vascular disease. It is in these "gray areas" where the limits are not well defined, and opportunities exist for expansion of pancreas recipient criteria. Please also note that T2DM—which was previously considered a relative, if not absolute, contraindication to pancreas transplantation—would no longer be considered in either of these categories. All candidates for transplantation undergo a comprehensive, protocol driven work-up that includes age-appropriate malignancy screening, cardiac and vascular evaluation, and screening for various infections [18]. Candidacy is determined through an evaluation process wherein referred patients are interviewed and/or examined by a social worker, dietitian, pharmacist, transplant physician (usually a nephrologist) and transplant surgeon. Surprisingly, an endocrinologist is often not part of this process because most patients are referred to the transplant center through a nephrology/dialysis unit pathway. The final decision with respect to candidacy is determined after all testing is completed and the patient is discussed in detail at a multidisciplinary listing conference.

Pancreas Transplantation Across the Spectrum of "Type"

Originally reserved only for patients with T1DM, SPK transplant has been increasingly offered to patients with T2DM owing to the excellent results achieved in this patient population over time [7, 25–27]. Conceptually, the terminology T1DM is used to describe patients with diabetes that do not produce insulin (usually from an autoimmune process) whereas T2DM is reserved for those patients who are "insulin resistant". Both populations exist on a spectrum of disease [27]. There are patients with T1DM that continue to produce insulin, but in insufficient quantities. Alternatively, there are patients with T2DM that stop producing insulin entirely. For this reason, defining the type of diabetes exclusively by C-peptide levels is inadequate, particularly in the setting of renal failure. Likewise, age of diabetes onset does not completely distinguish between the different types. Although most patients with T1DM are younger, this disorder can develop later in life. Conversely, there is also an increasing incidence of T2DM in younger patients. Body habitus also fails to categorically define type of diabetes because patients with T1DM may be overweight and patients with T2DM may be lean. Absence of diabetic ketoacidosis and initial therapy with non-insulin alternatives are also characteristic but not always exclusive to patients with T2DM. T2DM is also more prevalent in non-Caucasian patients but again race or ethnicity is not an absolute differentiating factor. Most confusing of all are those patients with T2DM who are managed exclusively with exogenous insulin administration and appear to do the same as patients with T1DM following SPK transplant [7, 25–27]. Finally, there is no rulebook dictating that every recipient can only be classified by a single category, so a patient that phenotypically appears to have T1DM may also develop insulin resistance and T2DM simultaneously. For this reason, the absence of endogenous insulin or presence of islet autoantibodies may solidify the diagnosis of T1DM but does not exclude a component of T2DM. Most centers that offer pancreas transplantation to candidates with a T2DM phenotype will generally set limits on BMI (<30–$32\ kg/m^2$), fasting C-peptide level (≤ 10–12 ng/ml), and total daily insulin requirements (<1u/kg/day or <100 u/day), although there have been isolated reports of successful pancreas transplantation performed beyond these guidelines [28, 29]. Because of older age, obesity, or co-morbidities, many centers in effect exclude the majority of patients with T2DM based on their standardized selection criteria [30]. It is important to note, however, that recipient selection is determined by clinical, psychosocial, and financial criteria rather than the "type" of diabetes. In other words, the recipient evaluation and selection processes are the same regardless of the presumed "type" of diabetes, which is largely irrelevant from an assessment perspective [31–33].

In addition to candidates with T1DM and T2DM, patients may be referred to transplant centers that have diabetes that defies both definitions and yet would benefit from transplantation. For example, patients that have undergone native total pancreatectomy for nonmalignant disease tend to exhibit particularly brittle diabetes due to the absence of all glucose homeostatic pancreatic hormones [34, 35]. These patients also struggle with exocrine insufficiency requiring supplemental oral enzyme replacement. If the allograft is drained enterically to the proximal intestine, pancreas transplantation not only renders the recipient euglycemic but will also improve gut absorption without the need for enzyme replacement. Another similar example is cystic fibrosis-related diabetes (CFRD), which has characteristics of both T1DM and T2DM and is frequently accompanied by exocrine insufficiency. For patients with cystic fibrosis and CFRD that are considered as potential candidates for lung or liver transplantation, it is reasonable to consider simultaneous or sequential pancreas transplantation because the recipient will require lifelong immunosuppression for the other transplanted allograft. Therefore, the only added risk is surgical related to the pancreas implantation, but the benefit of rendering the recipient normoglycemic and resolving their exocrine insufficiency is enormous [36–43].

Pancreas Transplantation for Non-Insulin Treated Diabetes?

The past two decades have been characterized by tremendous improvements and insights in the medical and surgical management of diabetes. For example, bariatric surgery now plays a key role in the management of obesity-related diabetes [44]. The introduction of newer insulin analogues, sophisticated insulin pumps, and continuous glucose sensors have raised the goals of conventional diabetes management and in combination provide the possibility of an artificial pancreas [45]. A profusion of newer oral medications or weekly injectable agents have dramatically changed the landscape of diabetes management and may offer side-benefits of weight loss and cardioprotective effects [46]. Diabetes is no longer strictly defined or thought of as either insulin-dependent or independent and the pathophysiology of diabetes should not be characterized by the treatment regimen. With the onset of progressive renal failure, some patients with diabetes become insulin-free and develop detectable C-peptide levels but can be managed successfully with non-insulin alternatives. Other patients may experience similar courses coincident with weight loss but still have diabetes. Particularly for patients with diabetes who are being evaluated for a kidney transplant, is the requirement of insulin therapy as a qualification for an SPK transplant still applicable? We know that virtually all these patients will return to insulin therapy following a successful kidney transplant alone because of the requisite change in renal function coupled with diabetogenic immunosuppressive agents. Similar to removing "type" of diabetes from consideration, the authors contend that the need for insulin therapy is an outdated qualification for pancreas transplantation and that the OPTN should remove this restriction to improve access to the waiting list for selected patients with non-insulin requiring diabetes who would otherwise clearly benefit from SPK transplantation.

Expanding the Criteria for Pancreas Transplantation: Age and BMI

In evaluating patients that are older or have a larger body habitus for pancreas transplantation candidacy, it becomes apparent that neither of the "numbers" associated with age and BMI in isolation completely capture the suitability of a candidate for pancreas transplantation. The literature consists mostly of low-quality evidence studies such as single center retrospective and registry analyses. These studies are limited by their retrospective nature and the fact that all included subjects underwent transplantation – establishing that these candidates were deemed suitable by the center's multidisciplinary team – introducing a selection bias. Taking this into account, it has been established that successful pancreas transplantation can be performed in patients that would have been deemed unsuitable in prior decades, but it is not clear exactly where the limitations exist.

Age is a chronologic construct that describes how long a patient has lived but does not necessarily reflect their current physiological and anatomical fitness and suitability for transplant. There are certainly older recipients that are in better physical shape than younger candidates. The literature for pancreas transplantation in older recipients (> 50 years of age in some studies, and > 60 in others) consistently demonstrates that pancreas transplantation is associated with progressively decreasing patient survival (related to older age, which itself is a risk factor for mortality) and similar allograft survival compared to younger patients [47–50]. In fact, some of these studies demonstrate inferior allograft survival in the youngest cohort of recipients, particularly when analyzing death-censored graft survival rates [50]. The most common etiology of allograft failure tends to be death with function in the older recipients as compared to acute and/or chronic rejection in the younger patients. However, having the allograft(s) outlive the recipient is not necessarily a negative outcome provided that the transplant did not lead to premature mortality. This data may suggest that the strength of the immunologic response to the allograft may decrease with senescence, or perhaps that compliance is a greater issue in younger versus older patients. Certainly, chronologic age alone should not determine suitability for transplantation. Functional status, frailty, sarcopenia, deconditioning, caregiver support, and comorbidities should be important considerations. Age does not correlate directly with frailty (especially in patients with diabetes), and despite efforts to quantify the latter, there are no clinically practical measures for standardized assessment of all patients and few studies that directly assess the impact of frailty on outcome after pancreas transplantation [51–55]. Although it is logical to presume that frailty is a risk factor for inferior outcomes following pancreas transplantation, it is not necessarily a contraindication exclusively. When compared to survival on dialysis or after kidney transplantation alone, older patients with diabetes continue to experience a survival benefit following SPK transplantation. Therefore, the goal of transplantation in general and SPK transplantation in particular is to ensure that patients do not experience an early death that is related either to the transplant procedure or requisite immunosuppression. This can be best accomplished by appropriate donor and recipient selection, meticulous surgical technique, and assiduous post-transplant care and monitoring.

Similarly, when considering body habitus, patients with identical BMIs may present with entirely different morphologic features depending on how their body weight is distributed. Limb loss, which is more common in this highly selected population of patients with diabetes than in the general population, also may render interpretation of BMI difficult. Several reports have described pancreas transplantation in patients with higher BMIs with mixed results. In general, similar survival outcomes have been reported but with higher operative risks and a higher incidence of complications such as fluid collections, surgical site infections, leaks, rejection, and incisional hernias [56–60]. Contrary to this data, registry studies have demonstrated decreased allograft and patient survival rates in recipients with obesity [61, 62]. These conflicting data suggest that transplantation of patients with high BMIs may be challenging and associated with inferior outcomes, but that similar outcomes to leaner recipients are achievable with increasing experience. It is critical that a surgeon evaluate the candidate's supine abdomen to determine if pancreas transplantation is feasible in patients with a higher BMI. Taller patients are less challenging than shorter patients with the same BMI because technical issues may be obviated by making a longer incision. Some patients with a high BMI carry their weight posteriorly (or in their extremities) and their abdomen flattens out when supine, which would facilitate safe pancreas transplantation. Imaging may also provide an assessment of external as well as visceral adiposity. Early reports suggest that robotic pancreas transplantation may also be an option for patients with obesity because obtaining adequate exposure and operating in a deep field are less of an issue [63]. Certainly, weight loss prior to transplantation would render the operation less challenging and would be the ideal solution rather than attempting transplantation on candidates with morbid obesity. There have been reports of successful pancreas transplantation following weight loss after bariatric surgery [64], and in the current era, many candidates are able to lose substantial weight with injectable medications such as the Glucagon-like-peptide 2 receptor agonists. The presence of uremia and initiation of dialysis, particularly hemodialysis, may lead to weight loss as well.

The authors encourage pancreas transplant programs to eliminate absolute upper limit cutoffs for age and BMI when considering candidates for pancreas transplantation. Rather, it is important to consider age and BMI within the context of other comorbidities, degree of frailty and fitness, and the results of evaluation testing, which would need to be completed anyway to assess candidacy for kidney alone transplantation. If there are opportunities to optimize the recipient prior to transplant (i.e., prehabilitation), these avenues should be pursued as well.

Technical Challenges: Reoperative Surgery and Retransplantation

Pancreas transplantation can be a challenging operation in any recipient, but the technical complexity is increased in the setting of prior laparotomies due to the unpredictable nature of adhesion formation. This is particularly of concern in cases of prior pancreas transplantation. In terms of early allograft failure, usually due to vascular thrombosis, there have been several studies that suggest that immediate or early retransplantation may be preferable to waiting because extensive adhesions have not yet formed [65, 66]. This approach allows placement of the new allograft into the same anatomic location as the prior failed transplant, thereby preserving other sites for possible future transplants. Although some indicate that this practice may be associated with a higher incidence of postoperative complications and rejection leading to premature loss of the second graft [67], most studies support immediate or early retransplantation and have demonstrated that it can be associated with similar allograft and patient survival rates compared to primary transplants provided that judicious donor selection is performed [65, 66, 68, 69]. The decision to retransplant the pancreas after a late allograft loss is more complex than in the immediate allograft failure scenario. If a pancreas transplant was initially indicated and the allograft has failed, the original indication persists, although the risk–benefit profile will now be leaning further towards a greater operative risk. It is clear from the literature that independence from both renal failure and diabetes is associated with a long-term survival advantage, in excess of that seen with kidney transplant alone [12]. It is likely that the operative exposure will be more difficult due to adhesions and the availability of suitable native vessels for implantation may be limited and more difficult to achieve. It is common to require additional procedures at the time of retransplantation including lysis of adhesions and allograft pancreatectomy or nephrectomy for nonfunctioning organs [70]. Sensitization after allograft failure, particularly in the setting of discontinuation of immunosuppressive medications, is another consideration that makes pancreas retransplantation more challenging from an immunologic perspective than the index transplant. Review of the literature for pancreas retransplantation yields many single center retrospective analyses with small cohorts of recipients [71–76] except for one study from the University of Minnesota with a large number of retransplants [77]. In most reports that compare pancreas retransplantation to primary transplants, excellent pancreas allograft and patient survival outcomes are reported. In those studies that also analyzed renal allograft survival, patients who underwent pancreas retransplantation after SPK transplant with a failed pancreas allograft had better renal allograft survival than those that did not undergo retransplantation [74], with outcomes similar to those following PAK transplant [76]. However, relaparotomy rates were quite high, ranging from 25–55% [71–73, 75]. It becomes evident from reviewing these studies that this is a very heterogeneous patient population with differences in the primary transplant performed (SPK, PAK, and PTA), which organs are being retransplanted (an isolated pancreas or both a kidney and a pancreas), and whether the initial pancreas and/or renal allografts had to be removed at the time of retransplant. Selection of a proper organ is critical as this is not an appropriate situation for utilization of a pancreas allograft from an expanded or non-idealdonor [78]. The published data comes primarily from high volume centers and the retransplant procedures were performed by experienced individuals. This operation requires a great amount of planning and can be technically quite challenging. By definition, a pancreas retransplant is reoperative surgery that usually requires a difficult dissection through scar tissue. Identifying a suitable target artery and vein for implantation is the primary goal prior to implantation and may require creative approaches such as using alternative vessels including the vena cava or iliac vein distal or proximal to the prior implantation site, the contralateral iliac artery, or the aorta. It is worth considering placement of ureteral stents to facilitate identification and preservation of these structures, particularly if allograft pancreatectomy or nephrectomy is considered at the time of retransplantation [79]. Occasionally, a complex vascular reconstruction may be required [80]. It is important to emphasize that although the indications for pancreas (and/or kidney) transplantation may remain the same with retransplantation, when compared to primary transplantation, the patients by design are older, chronically immunosuppressed, have had prior abdominal surgery, and may be sensitized. Therefore, patient selection is more restrictive compared to primary transplantation and shared decision-making with the patient is critical after a frank discussion of the unique risk factors associated with retransplantation.

Conclusion

Pancreas transplantation remains the only therapy that can predictably achieve sustained euglycemia independent of exogenous insulin administration in patients with insulin-treated diabetes. This procedure is most frequently performed in the setting of combined pancreas and kidney transplantation for patients with uremia and diabetes. The field of pancreas transplantation has evolved to offer this option to many patients that would not have been considered candidates previously, particularly for those that exhibit features of T2DM, are older or have a higher BMI (with or without weight reduction), present technically complex scenarios, or is performed in combination with other nonrenal organs. It is likely that, despite liberalization of these prior restrictions, even further expansion of the recipient pool is possible. It remains unclear whether we are on the verge of discovering that more patients with diabetes and chronic kidney disease might benefit from SPK transplant irrespective of age, size, diabetes type, or insulin need, or if it remains appropriate only for a select group of the diabetes population with uremia. Given that many potential pancreas transplant candidates are referred for evaluation to a kidney transplant center that is not experienced in pancreas transplantation, the question of regionalization of pancreas transplant services has been considered. With increasing experience, improving outcomes, and better access, the limits of feasibility for pancreas transplantation continue to evolve.

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