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Simultaneous pancreas and kidney transplantation: current trends and future directions

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Purpose of review
Important trends are being observed in pancreas transplantation in the USA. We will describe recent trends in simultaneous pancreas kidney (SPK) transplantation related to immunosuppression, treatment of rejection, and transplantation for patients of advanced age and C-peptide positive diabetes.

Recent findings
Rates of pancreas transplantation have declined, despite improved pancreatic graft outcomes. Regarding immunosuppression, trends in SPK transplantation include T-cell depletion induction therapy, waning mammalian target of rapamycin inhibitor use and steroid use in greater than 50% of pancreas transplant recipients with few patients undergoing late steroid weaning. Rejection of the pancreas may be discordant with the kidney after SPK and there is a greater appreciation of antibody-mediated rejection of the pancreas allograft. De-novo donor-specific antibody without graft dysfunction remains an active area of study, and the treatment for this condition is unclear. SPKs are being performed with greater frequency in type 2 diabetes mellitus patients and in patients of advanced age, with exemplary results.

Summary
The current state of the art in SPK transplantation is yielding superb and improving results.

Keywords
biopsy, donor-specific antibody, immunosuppression, kidney transplantation, pancreas transplantation, rejection, type 1 diabetes, type II diabetes

INTRODUCTION

Diabetes patients with chronic kidney disease (CKD) experience excessive morbidity and mortality [1]. Simultaneous pancreas and kidney (SPK) transplantation has been shown to significantly improve quality of life and increase life expectancy of uremic diabetes patients [2–5]. One-year and 5-year pancreas graft survival rates are now comparable with those of kidney, liver, and heart transplants [6]. In addition to improving results, important trends are being observed in the USA. In this review, we will describe recent trends in immunosuppression management, diagnosis and treatment of pancreatic allograft rejection, and transplantation for type 2 diabetes and patients of advanced age as they relate to SPK.

DECLINING PANCREAS TRANSPLANT RATES DESPITE IMPROVED OUTCOMES

Owing to a variety of factors including improved surgical technique, immunosuppression, donor and recipient selection, and graft surveillance – with greater reliance on pancreas biopsy – the half-life for an SPK pancreatic graft (Fig. 1) has steadily increased to over 14 years [7]. Registry data suggest that the majority of the improvement in long-term graft survival is because more grafts survive the first year posttransplantation, which is in part because of fewer early technical graft losses. Of the various forms of pancreas transplantation (solitary pancreas transplant [SPT] vs. SPK), SPK has historically been associated with better pancreatic graft survival [8].

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KEY POINTS

- Owing to improved surgical technique, immunosuppression, donor and recipient selection, and graft surveillance – with greater reliance on pancreas biopsy – the half-life for an SPK pancreatic graft has improved to 14 years.
- Late steroid withdrawal in SPK patients should be approached with extreme caution; rates of use of steroid avoidance have stabilized.
- At the University of Wisconsin, depleting antibody induction is used for patients with preoperative DSA; however, it is currently unknown what to do with de-novo DSA in the setting of normal pancreas allograft function.
- Excellent long-term patient and graft survival can be achieved in patients with T2DM and in patients of advanced age.

Between 1988 and 1998 rates of pancreas transplantation increased markedly worldwide, with SPK representing the vast majority of transplants. However, since the early 2000s, rates of pancreas transplantation have stabilized and even declined in the USA (Fig. 2). The reason(s) for this decline are not well understood [9]. The most pronounced decrease in volume was observed in pancreas after kidney (PAK) transplants, which may be due to changes in referral patterns. SPK transplant volume saw a plateauing or slight decline recently compared with the dramatic increases observed in the prior decade. The reason for the decline in SPK transplant volume is not precisely clear but is likely multifactorial. An analysis of the United Network for Organ Sharing/Scientific Registry of Transplant Recipients (UNOS/SRTR) database suggests that fewer patients are being placed on the SPK waiting list [10▪]. It has been suggested that decreased rates of SPK waitlisting may be related to changes in the rates of diabetic nephropathy development or delayed progression to later-stage CKD [11]. In this regard, greater availability of better insulin delivery systems and diabetes education are probably having a beneficial impact. However, regional waiting list rules may also be contributory. Declining rates of pancreas transplantation may also be reflective of more stringent donor selection and greater scrutiny of center outcomes. Finally, it is very likely that changes in the donor population are adversely affecting allocation of suitable pancreata. Only approximately 15% of US deceased donors in 2013 donated a pancreas for transplantation. This is not a surprising trend given that the US donor population is becoming increasingly old, obese, and diabetic [11]. Undoubtedly, some transplantable pancreata are also being allocated for islet transplantation and research. It would be of interest to understand whether other countries are observing similar trends to those occurring in the USA, alas these data are not readily available.

Fortunately, recent changes in the organ allocation policy in the USA should lessen the declining pancreas transplant numbers. With the new pancreas allocation system (PAS), SPK transplant recipients are placed on a separate waiting list, distinct from the kidney waiting list, and will have access to a kidney from every suitable pancreas donor. In addition, SPK, PTA, and PAK patients are now placed on one combined pancreas waiting list, and are given equal priority. The proposed changes may increase pancreas utilization for SPK recipients locally and regionally, more so than SPTs.

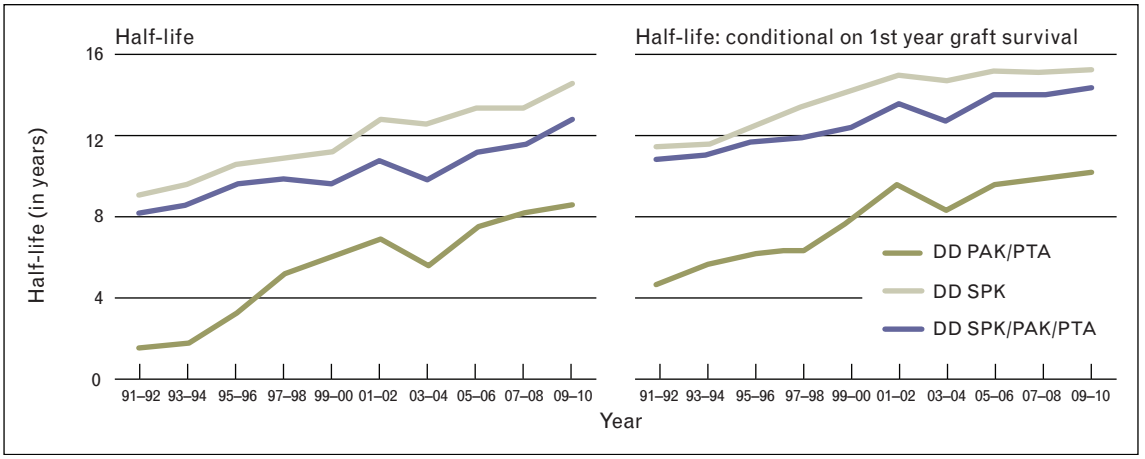

FIGURE 1. Improving results of SPK transplantation in the USA. The half-life for an SPK is now approximately 14 years. PAK, pancreas after kidney; PTA, pancreas transplant alone; SPK, simultaneous kidney pancreas. Reproduced with permission from [6].

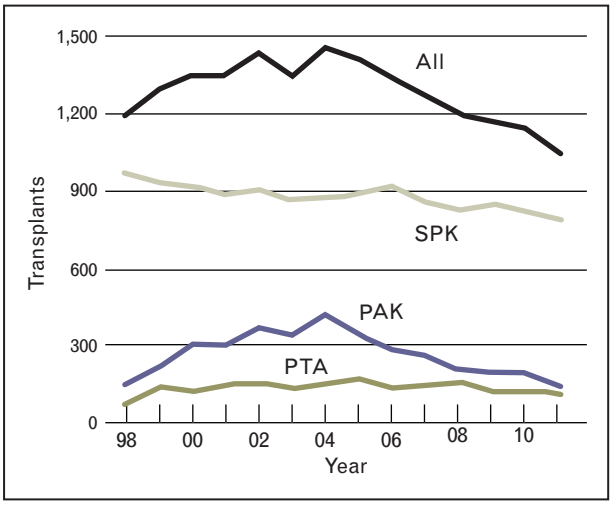

FIGURE 2. Decreases in pancreatic transplant volume. Although still the most frequent of all forms of pancreas transplantation, SPK volumes have decreased since the late 1990s in the USA. PAK, pancreas after kidney; PTA, pancreas transplant alone; SPK, simultaneous kidney pancreas. Reproduced with permission from [6].

Hopefully, these changes will reduce SPK waiting times and increase access to SPK transplantation. Furthermore, the new PAS makes pancreas allocation more uniform across the USA and disentangles pancreas allocation from kidney allocation.

ADVANCES IN IMMUNOSUPPRESSION

Immunosuppression protocols for SPK follow patterns similar to other solid organ transplants. Pancreas transplant recipients are believed to require higher levels of immunosuppression, possibly related to the increased immunogenicity of the pancreas, and/or autoimmune status of the recipient. Unfortunately, given the low-volume nature of pancreas transplantation, the evidence for advantages or disadvantages of specific immunosuppressive regimens is quite limited. Currently, most centers use induction therapy with antithymocyte globulin, alemtuzumab, or basiliximab [12,13]. Most SPK patients receive a depleting antibody agent, such as alemtuzumab or antithymocyte globulin [6,14] (Fig. 3). For maintenance therapy, more than 80% of SPK patients also receive tacrolimus and mycophenolate mofetil (MMF) [6,14]. Steroids are used in more than 60% of recipients, and steroid use is favored by some, but not all, centers, (see Fig. 3 for US trends in immunosuppression) [6]. Interestingly, steroid usage has increased slightly in recent years despite interest and positive results of small steroid avoidance trials. Very few patients are being weaned late or within the first year post-transplant. Additionally, very few current immunosuppressive protocols for SPK involve mammalian target of rapamycin inhibitors (Fig. 3). The standard regimen of antibody induction and maintenance with tacrolimus, MMF, ± steroids has ushered in an era of routine success in pancreas transplantation, with 1-year pancreas allograft survival approaching 90% [6,15]. That being said, there are many opportunities for refinement of immunosuppressive protocols.

Stratta *et al.* [16,17] recently reported the 5-year outcomes of a randomized study in SPK patients. The authors compared alemtuzumab induction with thymoglobulin induction and found similar patient and graft survivals [16,17]. There was a trend toward less-frequent acute rejection and, perhaps interestingly, fewer major infections in the alemtuzumab group [17]. This was a small study (46 patients, 28 in alemtuzumab arm), but the results are provocative, especially as centers become more cost-conscious. Alemtuzumab is less expensive than thymoglobulin, requires fewer doses, and does not require central venous access.

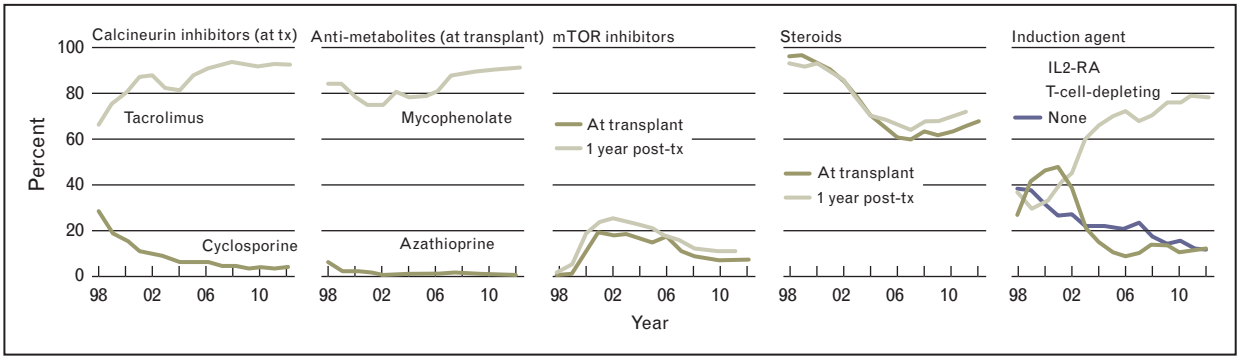

FIGURE 3. Trends in immunosuppression. T-cell-depleting agents are being used more frequently; mTOR inhibitors less frequently and steroid avoidance rates have stabilized. mTOR, mammalian target of rapamycin; IL2-RA, interleukin 2 receptor. Reproduced with permission from [6].

Long-term calcineurin inhibitor (CNI) use has been associated with transplant glomerulopathy leading to graft loss as well as direct beta-cell toxicity [18,19]. Consequently, strategies are being developed to minimize the reliance on CNIs in pancreas transplantation wherein either the native kidneys or transplanted kidney might be at risk. Belatacept is a selective costimulatory blocker, which unlike CNIs, avoids nephrotoxicity [20] and has not been associated with glucose intolerance or beta-cell toxicity to date. Mujtaba *et al*. reported their experience in two patients switching from CNIs to belatacept to prevent progressive CKD. Both patients weaned safely from tacrolimus to belatacept and sirolimus [21], and both enjoyed measurable improvement in renal function. Mirroring larger experiences in kidney transplantation [22], belatacept may prove an important strategy for preservation of renal and pancreatic function after SPK transplantation, either as a first-line or rescue therapy. Indeed, there is an ongoing belatacept induction and maintenance trial in primary SPK transplantation using maintenance MMF, early steroid withdrawal and CNI minimization with possible weaning (CTOT-15; NCT01790594). This ongoing study may yield practice-changing results, although the need for intravenous infusions and avoidance in Epstein–Barr virus naive recipients may somewhat limit its more widespread use.

Steroid side-effects are myriad and include hyperglycemia, hypertension, hyperlipidemia, increased risk of infection, obesity, cataracts, muscle disease, bone metabolism alterations, and skin problems. Each of these is a potential obstacle after SPK [23]. A recent Cochran review evaluated steroid avoidance and steroid withdrawal protocols in pancreas transplant recipients [24]. The authors concluded there is insufficient evidence to support steroid avoidance/withdrawal (both early and late) in available studies of pancreas transplantation, most of which involved SPKs. Extrapolations from the kidney transplant literature suggest that late steroid withdrawal should be attempted with extreme caution [25], which is reflected in the current low rate of late steroid withdrawal. There is probably little long-term benefit and a small, although clear risk observed in patients withdrawn from low doses (5 mg) of steroids. However, it is plausible that glucocorticoid avoidance will provide the best overall risk-to-benefit ratio in the SPK population. Some avoidance protocols are being used successfully, but long-term data are lacking. These protocols typically include antibody induction, tacrolimus, and MMF, although newer combinations are expected to be tested. Our center's steroid avoidance protocol involves alemtuzumab induction with MMF and tacrolimus maintenance.

Lastly, because compliance is a major obstacle to long-term outcomes, tacrolimus has been reformulated to be delivered once daily. Once-daily dosing decreases pill burden and may improve medication compliance. Falconer *et al.* [26] have demonstrated that conversion to this once-daily dosing of tacrolimus has proven safe and effective in the short term. Long-term outcomes with once-daily tacrolimus in pancreas transplantation are forthcoming.

ADVANCES IN DIAGNOSIS OF PANCREAS REJECTION

Niederhaus *et al.* [27▪▪] recently reported on the incidence, risk factors, and outcomes of rejection of the pancreas. The incidence of rejection within 1-year posttransplantation in a cohort of 162 patients of all pancreas transplant types, including many retransplants undergoing for-cause biopsies, was 21%, with antibody-mediated rejection (AMR), acute cellular rejection (ACR), and mixed rejection occurring in nearly equal frequency. In their study, the majority of pancreas rejection episodes were successfully reversed and graft function was maintained; however, 20% of grafts were lost within a year of diagnosis, which highlights the need for early diagnosis and efficient surveillance. Dong *et al.* [28] recapitulated this finding by showing that rejection was associated with subsequent graft failure. Risk factors for rejection identified in these two studies included nonprimary SPK transplant, primary pancreas transplant alone (PTA), race mismatch [27▪▪], and increasing donor age [27▪▪,28]. Increased vigilance for rejection and possibly surveillance biopsies in these scenarios may therefore be warranted.

A pancreas allograft biopsy allows the surgeon to accurately identify and define rejection, and should be incorporated into the portfolio of pancreas transplant monitoring. Reliance solely on clinical parameters such as hyperglycemia, serum amylase and lipase, C-peptide level, hemoglobin A1C, or (if bladder drained) urinary amylase are insufficient because they are either too late or nonspecific. The utility and cost–effectiveness of surveillance biopsies have not yet been studied.

Contrary to prior assumptions, concordance in pathology between kidney graft and pancreas graft biopsies after SPK transplantation is not 100% and grafts can exhibit differing types and degrees of rejection (unpublished results, JSO). Therefore, kidney biopsies alone for SPK patients are insufficient to determine the pathologic status of the pancreatic graft. Discordant results between a duodenal cuff biopsy and pancreas parenchymal biopsy also occur [29]. Furthermore, grading of duodenal

rejection has not been established and C4d staining is not reliable.

The most commonly performed biopsy technique at this time is percutaneous ultrasound-guided biopsy of the pancreatic parenchyma. This can be done in bladder-drained or enterically drained allografts safely and effectively. For example, at the University of Wisconsin, the complication rate is very low. Of 422 pancreas biopsies performed since 1994 at the University of Wisconsin, we have observed no biopsy-related graft losses and minimal morbidity.

DONOR-SPECIFIC ANTIBODY AS A NONINVASIVE BIOMARKER OF REJECTION

The deleterious effects of both preformed donor-specific antibodies (DSA) and de-novo DSA are well established for kidney transplantation [29]. Few studies, however, have directly evaluated the role of DSA in pancreas transplantation. Cantarovich *et al.* [30] showed that DSA in SPK transplants was an independent predictor of graft failure. In their study, 24% (40/167, 152 were SPK recipients) of the patients had DSA postoperatively. All were treated with antithymocyte globulin, tacrolimus, and MMF. No steroids were used as maintenance therapy. The authors identified DSA as an independent predictor of graft failure [30]. However, DSA was not quantified in all the patients preoperatively. As such, it is unclear who had preformed DSA vs. who developed de-novo DSA.

Mittal *et al.* [31] demonstrated in a large cohort of pancreas transplant patients that de-novo DSA was also an independent risk factor for graft loss. In this study of 439 pancreas transplant patients (73% SPK), de-novo DSA developed in 38% of patients. The immunosuppressive regimen consisted of alemtuzumab induction followed by MMF and tacrolimus, but without steroids. This is a surprisingly high rate of de-novo DSA and may have been due to the immunosuppressive regimen or other factors. There are reports of alemtuzumab being associated with increased DSA production in kidney transplant recipients, which may explain the ostensibly high incidence of de-novo DSA in the Mittal *et al.* [31] study. An improved understanding of DSA, B-cell biology, and the relevant mechanisms will be critical to the future success of SPK [32].

At the University of Wisconsin, the presence of pretransplant DSA aids our assessment of posttransplantation immunologic risk. For patients with pretransplantation DSA and a negative crossmatch, we favor a depleting antibody induction therapy. Posttransplantation, we monitor our patients with serial DSA measurements at a frequency determined by the preoperative risk assessment. However, it is currently unknown what to do with de-novo DSA in the setting of normal pancreas and kidney allograft function. One hypothesis is that it indicates under immunosuppression, and that increasing immunosuppression may be warranted. Elevated DSA in the setting of normal graft function could also be a harbinger of eventual graft dysfunction, or simply could be of no clinical consequence. If the emergence (or rise) in DSA accompanies abnormal graft function, then a biopsy is warranted to rule out rejection. Our clinical algorithm (Fig. 4) for treatment of pancreas graft dysfunction has been described previously [33].

TYPE 2 DIABETES

The primary indication for pancreas transplantation remains type I diabetes mellitus (T1DM), whereas type 2 diabetes mellitus (T2DM) remains a contraindication for transplantation in many centers in the USA, and around the world [1,10▪]. The pathophysiology of T2DM includes genetic causes of chronic inflammation and insulin resistance leading to hyperinsulinemia, which ultimately results in beta-cell exhaustion [34,35▪]. In contrast, T1DM patients classically suffer autoimmune-mediated damage to beta cells leading to decreased (or absent) insulin secretion. Thus, as beta cells become irreparably injured, beta-cell replacement becomes an appropriate therapy [36]. Given the increasing prevalence of T2DM in most western countries, and given that T2DM is among the leading causes of kidney disease, pancreas transplantation may be underutilized in this population. Currently, approximately 8% of SPKs in the USA are performed for T2DM, in contrast with 5 and 1% for PAK and PTA, respectively [10▪,14].

Making the precise diabetes diagnosis (T1DM vs. T2DM) can be difficult and is often not accurately determined by referring clinicians or by transplant centers. Although classical clinical findings are defined for both T1DM and T2DM, the diagnosis remains ambiguous in some cases. Obesity, and later age of onset, for example, often blurs the diagnosis between T1DM vs. T2DM. C-peptide has been used to distinguish T1DM from T2DM. Although some clinicians have based their diagnosis of T2DM purely on the presence or absence of C-peptide, this may not be the best indicator. In the context of renal failure, some groups have suggested that C-peptide levels be used to determine SPK candidacy [37], yet others feel the C-peptide level is immaterial and the general cardiovascular and metabolic status of the patient is more important. Complicating its clinical

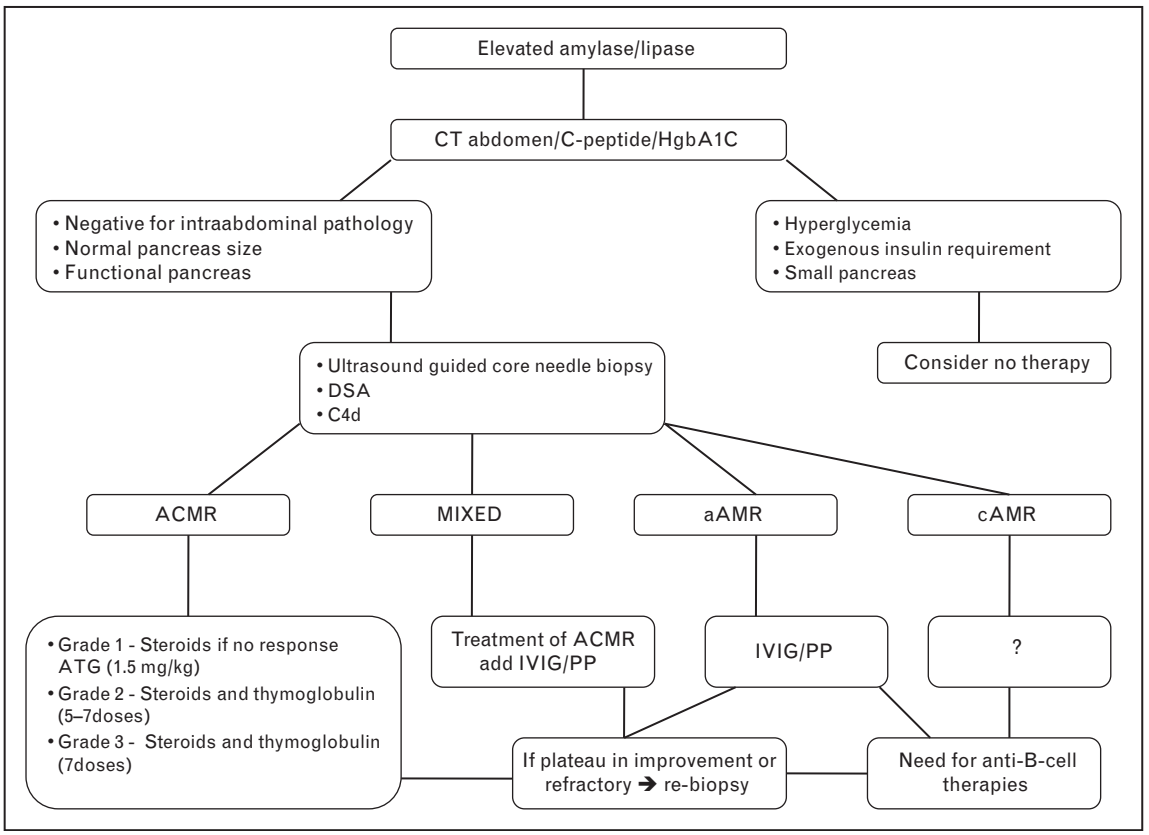

FIGURE 4. The University of Wisconsin treatment algorithm for pancreas allograft rejection. Pancreatic biopsy is critical to determination of treatment. aAMR, acute antibody-mediated rejection; ACMR, acute cell-mediated rejection; ATG, antithymocyte globulin; cAMR, chronic antibody-mediated rejection; DSA, donor-specific antibody; IVIg, intravenous immunoglobulin; PP, plasmapheresis. *Published in Trends in Transplantation, © Permanyer Publications [33].

utility, fasting C-peptide levels may be falsely high in patients with CKD and/or gastroparesis [37]. Additionally, C-peptide is not always positive in the T2DM patients, further confounding the diagnosis [38▪▪,39]. There is a clear need for more precise, multiparameter or genetic categorizations of T1DM, T2DM, and/or other forms of diabetes before transplantation.

Regarding the evaluation of T2DM (C-peptide positive) patients, some authors have advocated including blood glucose lability, insulin-dependence, diabetes mellitus duration of at least 5 years, BMI less than 32 kg/m^2, as well as absence of cardiovascular comorbidities to determine SPK candidacy [37]. SPK patient selection in T2DM may also require an evaluation of other therapies for T2DM such as lifestyle modification and bariatric surgery [36,40]. Most transplant physicians recommend avoiding patients with evidence of significant metabolic syndrome. Although high-risk renal and pancreas transplant candidates warrant aggressive cardiac investigation, some authors have recently challenged the utility of routine cardiac testing in the preoperative setting for liver and kidney transplantation [41]. At the University of Wisconsin, our approach to the T2DM SPK candidate is patient specific. Generally, our group will accept T2DM patients who are insulin-dependent, age less than 55, BMI less than 32 kg/m^2, have insulin requirements less than 75 U/day, have no (or minimal) coronary and iliac arterial disease, and do not exhibit signs and symptoms of metabolic syndrome [42,43▪▪]. Additionally, all SPK candidates undergo cardiac stress testing, and patients with concerning findings subsequently undergo coronary angiography. Although there is clearly a population of T2DM patients who benefit from SPK, the selection criteria is not uniform between centers [44].

In the past, researchers thought that because patients with T2DM had insulin resistance, they would suffer from beta-cell exhaustion and subsequently experience poor outcomes after pancreas transplantation [45]. Light *et al.* [39] helped to clarify the outcomes of T2DM (C-peptide positive) patients after SPK in a study evaluating the long-term results of 135 patients, of which 28% were T2DM. When data were stratified by diabetes mellitus type, there was no observed difference in patient or pancreatic graft survival [39]. Long-term (20-year)

data from the Light *et al.* [38▪▪] series also suggest similar patient and graft survival regardless of diabetes type after risk stratification. In another single-center review of SPK transplants from Europe published in 2013, authors identified 21 patients of 216 who were transplanted for a diagnosis of T2DM [46]. Authors found that T1DM patients differed from T2DM patients. Whereas three-quarters of T1DM patients did not have findings of vascular disease, three quarters of patients with T2DM did. Neuropathy was also more common in patients with T2DM. The most common cause of pancreatic graft loss was rejection in T1DM patients vs. patient death in T2DM patients. Importantly, patient and pancreas graft survival were not different at 5 years. Although authors observed lower patient survival (90 vs. 96%) in T2DM SPK patients when compared with T1DM SPK patients, overall patient survival in the T2DM SPK patients was superior to those patients undergoing kidney transplantation alone [46]. Taken together, there is clearly a group of T2DM patients who benefit from SPK, and both short-term and long-term outcomes are commensurate with T1DM patients.

SIMULTANEOUS PANCREAS AND KIDNEY IN PATIENTS OF ADVANCED AGE

Many centers are relutant to perform an SPK in patients older than 50 years of age [44,47,48] and according to the International Pancreas Transplant Registry, approximately 2% of pancreas transplants are performed in patients older than 60 years of age [1]. Data from 15–20 years ago suggested that pancreas transplantation was associated with greater morbidity and mortality when recipients were 45 years old, or older [49]. In the context of improved outcomes and the diabetes mellitus population living longer, older patients are now being listed for SPK [10▪]. In both renal and liver transplantation, the notion that age should be used to determine candidacy for transplantation has already been challenged [50,51].

In a study of both SPK and SPT published in 2014, investigators from the University of Indiana stratified patient and graft survivals by age [48]. In their experience, SPKs made up 63% of pancreas transplant procedures for those aged 30–39. A step-wise decrease in SPK frequency was seen for each subsequent decade of recipient age. In recipients older than 60 years ($n = 18$, 4% of study group) SPK comprised 44% of pancreas transplants. Authors observed no difference in graft survival and no increase in cardiac events in this group [48]. Not surprisingly, the older cohort had a longer history of diabetes mellitus. Cold ischemia times were lowest for this group of patients, possibly suggesting a surgeons' selection bias for placing ideal organs with low cold ischemia times in older recipients [48]. Patients in the oldest age strata (50–59 years and >60 years) had the lowest glomerular filtration rates after transplantation [48]. Additionally, when evaluating causes of graft loss, the oldest patients in the University of Indiana study were most likely to die with a functioning graft, whereas younger patients were more likely to experience immunological graft loss. The finding that older patients are less likely to experience rejection has been supported by other studies [52]. As such, the authors suggest that, in a sense, older patient's transition from a higher to lower immunologic risk, offset by a slightly increased operative and cardiac risk [48]. Nonetheless, these data are supportive that chronological age alone may not be appropriate for exclusion from pancreas transplantation candidacy.

Siskind *et al.* [53▪] published in 2014 a study of age-stratified pancreas transplantation outcomes using the UNOS/SRTR database. The authors identified 280 patients greater than 60 years old who underwent pancreas transplantation. Of these, 154 patients (51.8%) underwent SPK [53▪]. Investigators showed, perhaps not unexpectedly, that older patients had shorter patient survival. However, upon evaluation of death-censored graft survival, authors observed minimal difference between various age groups [53▪]. There was no difference in 1-year death-censored graft survival among any of the age groups. Those 40–49 years of age enjoyed 67.8% 5-year death-censored graft survival. In contrast, those aged 50–59 experienced 5-year death-censored graft survivals of 67.4% and those over 60 years of age experienced 5-year death-censored graft survivals of 59.9% [53▪]. However, patients aged 18–29 years old experienced 5-year death-censored graft survivals of only 56.8%. Taken together, surgeons in 2014 are more likely to transplant older recipients when compared with years past and, chronological age alone should not be used to determine transplant candidacy.

CONCLUSION

In conclusion, the current state of the art in SPK transplantation is yielding superb and improving results. Unfortunately, despite this, the number of pancreas transplants performed yearly in the USA has declined. Although the exact cause is not clear, it is likely multifactorial involving changes in recipient demographics (delayed progression to CKD in T1DM), and possibly changes in regional referral patterns accounting for lower numbers of waitlisted patients. SPK transplant rates have also declined paralleling these declines in waitlisting. Trends in worsening donor quality and increased surgeon selectivity for pancreata may also be contributing

to declining transplant trends. Nonetheless, solid organ pancreas transplantation generally achieves a superior level of durable euglycemia and quality of life for appropriately selected patients. Expanding access through modified pancreas allocation systems in the United States and patient advocacy efforts and continuing to improve outcomes of marginal grafts are the focus of current efforts. There are data to support the expansion of this therapy in appropriately selected T2DM and older patients. Furthermore, advances in CNI-free and steroid-free immunosuppression and immune monitoring will likely lead to even better patient and graft outcomes while minimizing unintended complications.

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None.

Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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