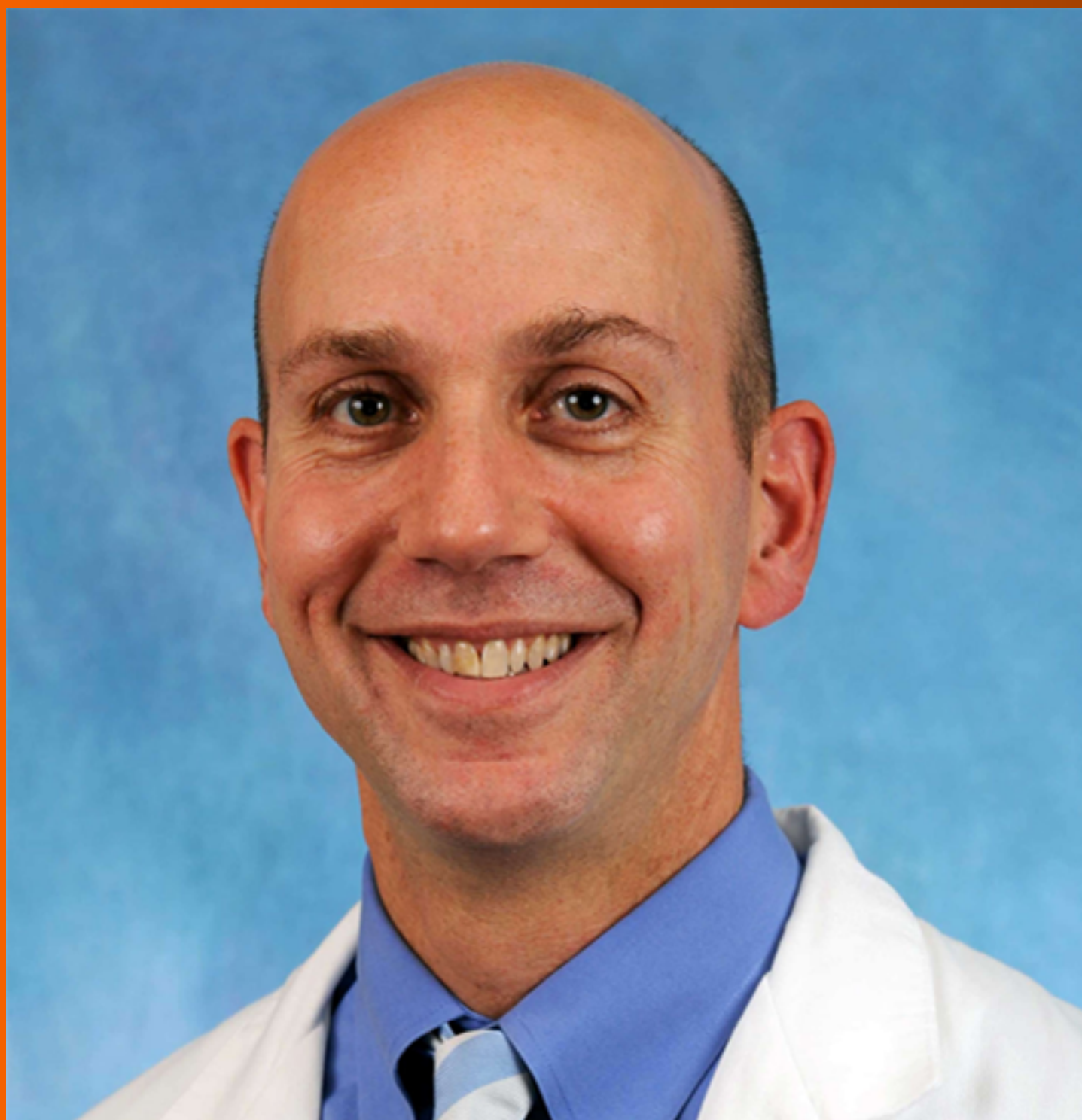


World Journal of *Transplantation*

World J Transplantation 2018 November 30; 8(7): 237-261





REVIEW

- 237 Solid pancreas transplant: Pushing forward
Giorgakis E, Mathur AK, Chakkeri HA, Reddy KS, Moss AA, Singer AL

ORIGINAL ARTICLE

Retrospective Cohort Study

- 252 Graft vs host disease impacts overall survival post allogeneic hematopoietic stem cell transplantation for acute lymphoblastic leukemia/lymphoma
Damlaj M, Snnallah M, Alhejazi A, Ghazi S, Alahmari B, Alaskar A, Al-Zahrani M

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Solid pancreas transplant: Pushing forward

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Abstract

Pancreas transplant has evolved significantly in recent years. It has now become a viable treatment option on type 1 diabetic patients with poorly controlled diabetes on conventional treatment, insulin intolerance, hypoglycaemia unawareness, brittle diabetes and/ or end-stage kidney disease. The purpose of this review is to provide an overview of pancreas transplant historical origins and current barriers to broader utilization of pancreata for transplant, with a focus on areas for future improvement to better pancreas transplant care. Donor pancreata remain underutilized; pancreatic allograft discard rates remain close to 30% in the United States. Donations after cardiac death (DCD) pancreata are seldom procured. Study groups from Europe and the United Kingdom showed that procurement professionalization and standardization of technique, as well as development of independent regional procurement teams might increase organ procurement efficiency, decrease discards and increase pancreatic allograft utilization. Pancreas transplant programs should consider exploring pancreas procurement opportunities on DCD and obese donors. Selected type 2 diabetics should be considered for pancreas transplant. Longer follow-up studies need to be performed in order to ascertain the long-term cardiovascular and quality of life benefits following pancreas transplant; the outcomes of which might eventually spearhead advocacy towards broader application of pancreas transplant among diabetics.

Key words: Pancreas transplant; Whole pancreas transplant; Donations after cardiac death pancreas transplant; Obese pancreas donors; Pancreas transplant for type 2 diabetes

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Core tip: Pancreas transplant has become a viable treatment option on type 1 diabetics. The purpose of this review is to describe current barriers to broader pancreatic allograft utilization, and focus on areas for future improvement. Donor pancreata, especially Donations after cardiac death (DCD), remain underutilized. Procurement professionalization might decrease discards and increase pancreatic allograft utilization.

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Pancreas procurements should be extended to DCDs and suitable obese donors. C-peptide positive non-obese brittle diabetics may be suitable transplant candidates. Longer studies on pancreas transplant cardiovascular benefits are needed; this might eventually drive pancreas transplant advocacy among diabetics.

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BACKGROUND

In 1894, Williams^[1] reported the implantation of minced sheep's pancreas to a 15-year-old diabetic boy for the treatment of his ketoacidosis. In 1922, Banting *et al*^[2] reported the use of pancreatic extract to treat diabetes mellitus (DM) in human, seemingly heralding the end of this scourge for all time. The discovery of insulin detracted from pancreatic transplant until 1966, at which time Kelly and Lillehei performed the first simultaneous human kidney-pancreas allotransplant from a deceased donor into a 28-year-old woman at the University of Minnesota, 3 years after the first reported kidney allotransplant^[3]. The first living donor pancreas transplant was performed at the University of Minnesota, in 1979^[4].

Other early efforts included islet cell transplant. Ballinger and Lacy demonstrated islet of Langerhans' isolation and subsequent *in vivo* post-transplant function in rats in 1972^[5]. Najarian and Sutherland performed the first clinical islet transplant in 1974^[6]. Further subsequent efforts culminated in the introduction of the Edmonton Protocol for islet cell transplant by Shapiro *et al*^[7] in 2000.

According to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR), as of end of 2014, over 48000 pancreas transplants were reported internationally, with approximately 29000 transplants performed in the United States alone^[8]. Nonetheless, pancreas transplant rates have declined in the United States by 33% from 2004 (approximately 1500) to 2014 (approximately 1000)^[9]. Similar trends were identified in the Organ Donation and Transplant (ODT) report in the United Kingdom^[10]: during 2015-2016, the total number of pancreas and kidney/pancreas transplants decreased by 37.9% and 3.5% respectively.

Paradoxically, this pancreas transplant decline has occurred despite of reported improvements in graft and patient survival outcomes. According to the Organ Procurement and Transplant Network (OPTN)/ Scientific Registry of Transplant Recipients (SRTR) 2014 Annual Data Report, graft and patient survival improved^[8]. These positive outcomes were attributed to improvements in recipient and organ selection, introduction of T-cell depleting agents for immunosuppression induction, and combined use of tacrolimus and mycophenolate mofetil for maintenance immunosuppression^[11].

In an era of an increasingly aggressive approach in other solid organ transplant categories, the transplant community seems to have remained conservative with pancreas allograft utilisation, at least within the United States territory^[9]. This is presumed to be multifactorial^[12].

Aim of this review is to outline the current pancreas transplant status, address barriers in pancreas donation and transplant, and describe ways to optimise pancreatic allograft utilisation and transplant of previously considered as unconventional pancreas transplant candidates.

Indications and types of pancreas transplant

Pancreas transplant has become an accepted treatment modality for both uremic and non-uremic patients with type 1 diabetes mellitus (T1DM). Pancreas transplant restores glucose homeostasis, relieving the patient from the need of ongoing glucose monitoring, insulin injections and the risk of life-threatening diabetic hypoglycemia or ketoacidosis. Nonetheless, considering the transplant-related morbidity and mortality plus the lifetime need for immunosuppression, not all T1DM patients should be considered for pancreas transplant.

Pancreas transplant has also become a viable option on T1DM patients with poorly controlled diabetes despite conventional treatment, insulin intolerance,

hypoglycaemia unawareness, brittle diabetes or end-stage kidney disease. There are currently 7 types of pancreas transplant: (1) simultaneous pancreas and kidney transplant (SPK). As per UNOS guidelines, SPK is indicated for T1DM patients or those with detectable C-peptide levels [as a surrogate indicator of type 2 diabetes mellitus (T2DM)], who are insulin dependent, have a body mass index (BMI) < 30 kg/m², and end stage renal disease, who are currently on dialysis or expected to require dialysis within 6 mo^[13]; (2) pancreas transplant alone (PTA), indicated primarily for T1DM with hypoglycaemia unawareness, non-compliance with insulin treatment and/or impaired quality of life and adequate glomerular filtration rate to render the need of kidney transplant unlikely^[14,15]; (3) pancreas-after-kidney transplant (PAK), indicated for patients who would qualify for a PTA and already have a viable renal allograft^[16,17]; (4) simultaneous deceased donor pancreas and live donor kidney transplant, indicated for patients who would qualify for SPK. This approach is expected to result in reduced waiting times, lower delayed graft function (DGF) rates and better outcomes^[18]; (5) total pancreatectomy and islet cell autotransplant (TPIAT). According to the PancreasFest consensus, TPIAT is indicated in selected patients with intractable pain related to chronic pancreatitis despite other appropriate treatment modalities, and no psychosocial or medical contraindications^[19]. In the United States, TPIAT is subject only to regulation of human cells and tissues (the tissue rules). The centers performing it should be registered with the Federal Drug Administration (FDA) and follow the Current Good Tissue Practices, without being required to submit FDA drug application^[20]; (6) laparoscopic donor distal pancreatectomy for living donor solid pancreas or islet allotransplant and pancreas-kidney transplant^[21,22]; and (7) islet allotransplant. The implantation of deceased donor islets of Langerhans is a promising treatment for T1DM with labile diabetes, recurrent hypoglycaemia and hypoglycaemia unawareness^[19]. In the United States, islet cell allotransplant is currently investigational and subject to both the FDA published guidelines on the tissue rules and the biologic and drug provisions.

SPK is by far the commonest pancreas transplant type. According to the SRTR data (United States), in 2014, 77% of pancreas transplants were SPKs, while PAK and PTA accounted for 13.6% and 9% of the transplants performed, respectively^[8].

Outcomes

According to IPTR, in 2007, PTA, SPK and PAK 1-year unadjusted patient survival was 95%-97%; the 5-year survival was 91%, 87% and 83%, respectively. PTA recipients were by definition non-uremic. These findings raised the question whether T1DM patients benefit from a pancreas transplant over a kidney transplant alone. Gruessner *et al*^[23] assessed mortality of pancreas transplant recipients over those on the waiting list (WL). Transplant recipients had elevated hazard ratios in the immediate post-transplant period up to 3 mo post-transplant^[23]. However, 4 years' follow-up showed SPK patient survival benefit compared to WL (90% *vs* 59%). PAK and PTA survival benefits were indeterminate in 4 years, possibly because WL mortality in these cohorts was lower due to their non-uremic status and younger age (PTA)^[23].

On their mortality assessment, Gruessner *et al*^[23] reported that, kidney allograft failure after SPK/PAK increases patient death risk by eleven-fold. The pertinent question remains whether these patients benefit from a functioning pancreas allograft. Most studies provided conflicting reports, partly due to insufficient follow-up and dependence on registry data^[24-30]. Morath *et al*^[31,32] (Heidelberg University, Germany) performed a very long term follow-up analysis based on the International Collaborative Transplant Study and observed that SPK graft and patient survival allograft outcomes were equivalent to living donor kidney transplant (LDKT) outcomes at 10 years; and, most importantly, that very long term survival (18-20 years) was superior among the SPK over the kidney transplant alone (on both LDKT and deceased donor kidney transplant recipients). The authors also noted decreased long-term cardiovascular events among the SPK patients^[31,32]. These findings should trigger extension of follow-up analysis across more pancreas transplant centers.

It remains unclear if re-establishment of long-standing euglycemia can halt or reverse end-organ diabetic complications. Fioretto *et al*^[33] estimated that a period of 10 years of euglycemia is a necessary interval to reverse diabetic nephropathy features.

DONOR PANCREATA

Current status

Across the United States, transplant surgeons often appear reluctant to consider pancreas allografts from donors considered as marginal for pancreas donation. As marginal are characterized older (> 50 years of age), obese, and donation after cardiac

death (DCD) donors. According to OPTN/UNOS, between 2003 to 2014, there has been a decrease in donors aged over 50, with 83% of donors aged less than 35 years^[8]; among the organs recovered, there were more recorded pancreatic discards from donors 50 years or older^[8]. During the same period, obese pancreas donors decreased from 56.3% to 34.6%^[8]. These findings may indicate diminished intent to use pancreata from marginal donors^[8].

Expanding the pancreas donor pool

According to the OPTN/ SRTR 2016 Annual Data Report, since implementation of the new pancreas allocation system in October 2014, there has been an increase in the number of pancreas transplants for the first time over a decade^[34]. At the same period, total active listings have also decreased, reaching a historic low^[34]. Despite the above, the average WL times have remained largely unchanged, with 34.2% of patients waiting between 1 and 3 years^[34]. Even though WL mortality has improved marginally over the recent years, there is still remarkable geographical variation across the United States, ranging from 0 to 15%^[34]. At the same time, pancreas transplant programs have become more liberal with their candidates' selection, as indicated by an increased proportion of T2DM patients (9.9% in 2016), of recipients aged over 50 years, and of candidates with higher BMI^[34]. Unless the pancreas donor pool is expanded, this more aggressive approach is expected to attract increasing numbers of transplant candidates and stretch the WL times further. In order to restrain WL times, decrease WL mortality and eliminate regional disparities in pancreas transplant access, it is necessary to expand the pancreas donor pool and increase pancreas transplant rates.

Utilization of pancreatic allografts from obese donors: Steatosis is a primary concern in evaluating pancreas allograft quality^[35]. The effect of steatosis on the pancreas allograft is presumably twofold: first, macrovesicular pancreatic steatosis may result in microvascular occlusion and thrombosis; second, adiponecrosis can potentially trigger inflammation and post-reperfusion graft pancreatitis^[35,36]. Donor obesity, the latter defined as donors with BMI of 30 kg/m² or greater, is a surrogate indicator of pancreatic steatosis; as such, obesity has been associated with poor pancreas transplant outcomes. For this reason, transplant centers commonly decline pancreatic allografts from obese donors. An OPTN database analysis of 9916 SPKs performed during period 2000-2013 compared the effect of donor BMI on graft outcome. The donors were categorized into 4 BMI groups: 20-25, 25-30, 30-35, and > 35 kg/m². BMI 20-25 kg/m² donor outcomes were compared to the rest of the groups. Only BMI > 35 kg/m² was associated with inferior kidney and pancreas allograft survival. BMI 30-35 kg/m² did not affect 3 mo, 1-, 5-, and 10-year kidney and pancreas graft survival. The authors concluded that pancreata from donors with BMI 30-35 kg/m² might be used safely for transplant^[37]. Certainly, this retrospective analysis is skewed due to potential discards upon visual of organs with significant interacinar fat infiltration or evidence of acute or chronic inflammation.

DCD pancreas utilization: DCD allografts have been used successfully in liver and kidney transplant. The concept of DCD pancreas transplant is not new; it has become an increasingly common practice in several European countries and the United Kingdom^[38,39]. In the latter, DCD pancreas transplant accounts for up to 19.5% of transplanted pancreatic allografts^[38]. However, in the United States, DCD pancreatic donation has remained out of favor, accounting for as low as 1.5 % of transplanted pancreata over period 1996 to 2014^[40].

Various studies have compared DCD *vs* DBD pancreas transplant outcomes (Table 1). The University of Wisconsin has been pioneering DCD pancreas utilization in the United States, reporting no difference in graft survival, function, complication or rejection rates between DBD and DCD pancreata; even though it did report longer renal DGF in the DCD cohort^[41-43]. Similarly, an OPTN/UNOS registry analysis by Salvalaggio *et al*^[44] reported comparable outcomes, even though DCD SPK recipients had longer hospital stay and, not unexpectedly, more protracted renal allograft DGF. The Oxford group performed a United Kingdom registry analysis which reported equivalent patient and graft survivals among 134 and 875 pancreas transplants performed between 2006 and 2010^[45]. A systematic review and meta-analysis published by Shahrestani *et al*^[46] in 2017 reported no difference in 10-year survival among the DCD and DBD cohorts. Kopp *et al*^[39] (Leiden University Medical Center, Netherlands) recently published a single-center cohort study, which indicated comparable outcomes among DCD and DBD pancreas transplants. The DCD donors were younger. The authors concluded that donor age was the most significant allograft survival prognosticator; therefore, younger DCD grafts might be a better option than DBD grafts from older donors^[39].

Table 1 Studies comparing pancreas transplant outcomes between donations after cardiac death vs donation after brain death pancreas allograft recipients

| First author/ yr | Country | Type of study | No. transplants | Mean donor age (yr) | Donor BMI [Median, IQR] | Warm ischemia time (min) | Cold ischemia time (hours) | Follow-up (yr) | Comments/c onclusions |
|--|----------------|----------------------------|------------------|---------------------|-------------------------|--------------------------|----------------------------|----------------|---|
| D'Alessandro <i>et al</i> ^[41] , 2004 | United States | Cohort | 31 DCD; 455 DBD | Unclear | ns | 15.3 (SD ns) | 15.9 (SD ns) | 5 | No difference in 5-yr graft survival in SPKs |
| Fernandez <i>et al</i> ^[43] , 2005 | United States | Cohort | 37 DCD; 539 DBD | 31 | ns | 17.5 (SD = 9.9) | 15.8 (SD = 3.4) | 5 | Indistinguishable patient and graft 5-yr survival in SPKs. Elevated DGF rate on DCD kidneys, with no significant long-term impact. |
| Salvalaggio <i>et al</i> ^[44] , 2006 | United States | Cohort; OPTN/UNOS Registry | 57 DCD; 3948 DBD | DCD= 30.1; DBD = 29 | ns | ns | 15.7 | 5 | For SPK recipients, the wait for DCD organs was shorter. DCD SPK recipients had longer hospital stay. Renal DGF was higher with DCD organs. Higher thrombosis rates (12.8% vs 6.1%) |
| Bellingham <i>et al</i> ^[42] , 2011 | United States | Cohort | 72 DCD; 903 DBD | DCD= 30 | ns | 20.8 (SD = 9.4) | ns | 10 | No difference in surgical complications, rejection or hemoglobin A1c levels. |
| Muthusamy <i>et al</i> ^[45] , 2012 | United Kingdom | Cohort | 134 DCD; 875 DBD | DBD = 32; DCD= 28 | 23 | 12 | 12.5 | 1 | Similar patient and graft survival, with improved DCD pancreas graft survival if performed as an SPK. Early graft loss in the DCD cohort was mainly due to thrombosis (8% vs 4%) |

| | | | | | | | | | |
|---|-----------------|-------------------------------------|--|--------------|--------------|-------------|-------------|--------|--|
| Shahrestani <i>et al</i> ^[46] , 2017 | Australia | Systematic review and meta-analysis | 762 DCD; 23609 DBD (included 10 cohort studies and 8 case reports) | DBD = 37 ns | 21-25 ns | ns | ns | 0.3-15 | No significant difference in 10-yr graft or patient survival. Higher graft thrombosis risk with DCDs [95% CI: 1.04-2.67; <i>P</i> = 0.006]. Thrombosis risk not higher when DCD donors were given ante-mortem heparin (<i>P</i> = 0.62) |
| Kopp <i>et al</i> ^[39] , 2018 | The Netherlands | Cohort | 21 DCD; 83 DBD | ^a | ^a | 31 (median) | 11 (median) | 5 | Without the DCD factor, PDRI from DCD donors was lower. Donor age was the only donor-related risk factor associated with graft survival. Post-op bleeding and renal DGF were more common with DCDs. Graft survivals were comparable. DCD pancreata had lower thrombosis incidence. DCD donors yield similar outcomes for low PDRI. Most DCD donors were younger. DCD grafts may be a better option rather than older DBD donors. |

^aRange not significantly different between DCD *vs* DBD donors. BMI: Body mass index; SD: Standard deviation; ns: Not stated in the study; DCD: Donation after cardiac death; DBD: Donation after brain death; SPK: Simultaneous kidney-pancreas transplant; DGF: Delayed graft function; PDRI: Pancreas donor risk index.

Graft thrombosis has been the DCD pancreas transplant Achilles heel. DCD pancreatic allografts appear to be more vulnerable to ischemia-reperfusion injury due to sustained peri-procurement ischemic insult, which may predispose them to higher risk of graft thrombotic events, even though its impact on overall graft survival has not been demonstrated yet^[39]. OPTN/UNOS registry analysis published in 2006 did demonstrate higher thrombosis risk in the DCD cohort (12.8 *vs* 6.1%)^[43]. Shahrestani *et al*^[46] meta-analysis has estimated that the odds of graft thrombosis were 1.67 times higher in DCD organs; however, that thrombosis risk was not significant if the donors had been given ante-mortem heparin^[45]. Interestingly, Kopp *et al*^[39] reported lower DCD graft thrombotic risk.

Professionalization and standardization of the pancreas procurement process:

According to SRTR, 27.7% of pancreata were discarded after recovery^[47], often due to pancreatic trauma occurring at the time of procurement. Ausania *et al*^[48] performed a retrospective ODT Registry analysis, and demonstrated that pancreatic allografts are indeed more vulnerable to procurement damage. More than 50% of recovered allografts had at least one reported injury, most commonly a short portal vein^[48]. Arterial and parenchymal damage were associated with higher graft loss risk^[48]. DCD status was not related to graft damage; increased BMI, aberrant hepatic artery anatomy, concurrent liver donation, and non-pancreas transplant procurement team increased the risk of pancreatic injury^[48]. The Dutch Transplant Foundation (DTF) developed a digital scoring system for abdominal organs donated and accepted in the Netherlands. According to DTF, pancreatic injury was reported in 25% of the recovered organs, of which only 2% led to organ discard^[49]. The authors identified higher donor BMI and DCD status as risk factors associated with organ discard due to procurement-related injury (Table 2)^[49].

The same research group (Leiden University Medical Center, Netherlands) also reported that organ recovery from surgeons accredited on standardized abdominal organ procurement methods, who also performed pancreas transplants in high-volume centers, was associated with more frequent recovery of the pancreas from DCD donors, less discards due to organ damage, and higher overall pancreatic allograft utilization^[50]. They developed a course named “Multi Organ Donor Procurement Surgery”, which has since been assimilated by the European Society for Organ Transplant^[50]. Aim of this course is to standardize abdominal organ procurement surgery training, including a step-by-step e-learning module and hands-on training, with documented completion of a set number of procurements under supervision and examination before certification^[50]. A same approach has been recently introduced and endorsed by the ODT in the United Kingdom.

The Netherlands is divided in 5 fully independent regional organ procurement teams, which procure all abdominal organs at their respective regions. Each of these teams consists of at least one certified surgeon, an assistant, two procurement scrub nurses and anesthesia team, and carries all necessary instruments to the donor hospital^[49]. Similarly, procurements in the UK are performed by regional independent organ procurement teams, each manned by at least one certified procurement surgeon, procurement scrub nurses/perfusionists, carrying their own surgical equipment to the site of donation. This procurement model results in standardization of the procurement technique and eliminates the donor hospital-related hazards (such as lack of appropriate equipment or non-acquaintance of the local scrub team to the demands of a multi-organ, especially a DCD, procurement). It further mitigates the inter-surgeon variation on the procurement technique and therefore procurement quality, degree of organ damage, and derivation of organ description to the receiving transplant surgeons. It also results in better team coordination and time management and, therefore, more efficient execution of the procurement surgery, both of which are critical factors for a successful rapid DCD organ procurement^[49,51]. Finally, this procurement model may lead to more experienced surgeons, and therefore, higher procurement quality and potentially less discards^[49-51].

The outcomes of the Dutch (DTF) and United Kingdom (ODT) procurement models indicate that pancreatic allograft utilization may be optimized and pancreatic discards minimized with standardization of the procurement technique and development of independent organ procurement teams, which should be organ procurement organization rather than transplant center-based. In the United States, standardization of the procurement technique and formal credentialing of procurement surgeons may be achieved *via* institutional initiatives and through the American Society of Transplant Surgeons; based on the European and United Kingdom experience, this may result in higher procurement quality, less discard rates, and increased procurement and utilization of DCD pancreatic allografts for the purpose of whole organ or islet transplant (Table 2)^[49-51].

Pancreas transplant centralization: A study published in 2017 by Kopp *et al*^[52] on the outcomes of 1276 pancreas transplants in the Eurotransplant region, demonstrated that patient and graft survival after pancreas transplant are superior in higher volume centers; the outcomes remain superior even after using organs with the higher Pancreas Donor Risk Index (PDRI). An OPTN/ UNOS study published in the same year, indicated better pancreas survival rates at high-volume centers across all PDRI categories (Table 2)^[53]. PDRI is a predictive model described by Axelrod *et al*^[54] in 2010, that may be used at the time of organ offering, in order to better assess which allografts would be associated with good survival. Identified risk factors were increased donor age, DCD and black race^[54]. In the United Kingdom, PDRI has been validated as a tool to predict survival in SPK transplant, but not in PTA or PAK transplant^[55].

Table 2 Studies on the effect of pancreas procurement professionalization and center volume on pancreas transplant outcomes

| First author, yr | Study aim | Region, country | Study period | No. cases | Results/comments |
|---|---|---------------------------------|--------------|---|--|
| Boer <i>et al</i> ^[49] , 2017 | Analysis of abdominal organ procurement quality and clinical impact. | Eurotransplant, The Netherlands | 2012-2013 | 591 procurements | 13% surgical injuries on procured pancreata, leading to 3% pancreas discards. Higher BMI, DCD donation in liver procurement were risk factors for discard due to injury. High procurement volume centers were associated with less pancreatic injury. |
| Lam <i>et al</i> ^[50] , 2017 | Analysis on the effect of the abdominal recovery team professionalization on the pancreatic procurement injury and acceptance for transplant. | Eurotransplant, The Netherlands | 2002-2015 | 264 procurements | 31.8% pancreatic surgical injuries. 85.6% of procured pancreata were eventually transplanted. Surgeons certified in abdominal organ procurements recovered more grafts from older donors, DCDs, and had less surgical injuries. Predictors to proceed with pancreas transplant were: certified procurement surgeons; surgeons from a pancreas transplant center; DBD donation; and lower donor BMI. Procurement certification results in less surgical damage and more pancreata transplanted. |
| Kopp <i>et al</i> ^[52] , 2017 | Analysis of the effect of the transplant center volume on pancreas transplant outcomes. | Eurotransplant, The Netherlands | 2008-2013 | 1276 pancreas transplants | Centers were classified into: low (< 5 transplants/yr); medium (5-13/yr); high volume (≥ 13/yr). Patient and graft survival were superior in higher volume centers. High center volumes were protective for graft failure, even though they transplanted organs with higher PDRI. |
| Alhamad <i>et al</i> ^[53] , 2017 | Analysis of the effect of the transplant center volume on the pancreas allograft failure risk. | UNOS, United States | 2000-2013 | 11568 SPKs and 4308 solitary pancreas transplants | Centers were categorized into low, medium, and high tertiles. Low volume centers were associated with higher pancreatic failure risk. High volume centers had better graft survival rates irrespective of PDRI. |

BMI: Body mass index; DCD: Donation after cardiac death; DBD: Donation after brain death; PDRI: Pancreas donor risk index; SPKs: Simultaneous kidney-pancreas transplants.

Living donor segmental pancreas transplant: SPK candidates are often advised to pursue LDKT, followed by PAK^[56]. Inevitably, this exposes the recipient to two operations. The SPK option from a living kidney-pancreas donor has also been advocated^[56-59]. This offers a pre-emptive kidney transplant, thus abolishing dialysis-related morbidity and mortality; allows the recipient to forego a second transplant operation (PAK); decreases the historically high early rejection risk-since the recipient

will be exposed to a single donor rather than two.

Living donor pancreatectomy was the first extrarenal organ to be successfully transplanted^[59]. The first living donor pancreas transplant was performed at the University of Minnesota, in 1979^[4]. According to Kirchner *et al*^[59] between 1994-2013, 46 living donor segmental pancreas transplants have been performed, with 0% mortality. 15% of donors developed post-donation DM requiring oral hypoglycemics, and 11% developed insulin-dependent DM. A risk stratification model for post-donation DM using 3 pre-donation risk factors (oral glucose tolerance, basal insulin and fasting glucose) and 1 post-donation risk factor ($\Delta\text{BMI} > 15$) predicted 100% of donors who developed post-donation DM^[59]. In conclusion, living donor segmental pancreas transplant is a viable option, after appropriate donor selection.

PANCREAS TRANSPLANT CANDIDATES

Conventionally, pancreas transplant is intended to restore function of the endocrine portion of the pancreas, in effect restoring normoglycemia in diabetic patients devoid of insulin producing capacity, *i.e.*, T1DM patients, especially those with labile or brittle diabetes, poor response or low compliance to insulin therapy, hypoglycemia unawareness, and/or renal failure. According to the SRTTR, in 2014, 9.2% of these transplants were performed on T2DM patients, increased from 7% in 2010^[60]. In 2016, T2DM pancreas recipients increased further to 9.9%^[34].

On this latter part of this review we will endeavor to explore the potential of pancreas transplant application to previously considered “unconventional” pancreas transplant candidates, such as T2DM (“C-peptide positive”) patients, overweight and mildly obese T1DM patients, and patients with chronic pancreatitis.

The C-peptide positive recipient

Pancreas transplant on T2DM contradicts traditional wisdom. T2DM has been attributed to insulin resistance rather than low or nil insulin production; in the presence of insulin resistance, pancreas transplant will arguably confer little or no benefit upon the recipient. There is also the potential to harm: pancreas transplant carries a high complication risk in a population with a multitude of inherent comorbidities; and, it places the transplant recipient under obligatory lifetime immunosuppression. Lastly, pancreas transplant on a T2DM may result in the waste of a precious commodity and the opportunity cost of its use on a T1DM patient.

Multiple studies have attempted to explore the effect of C-peptide presence on SPK outcomes (Table 3)^[61,62,64-66]. Stratta *et al*^[62], performed a single center retrospective analysis of 162 SPK patients, including 30 (18.5%) of C-peptide positive (C-peptide levels ≥ 2.0 ng/mL) *vs* 132 C-peptide negative patients. In a mean follow-up period of 6.5 years, there were no differences between the two groups in terms of patient, pancreas and kidney graft survival, acute rejection, HbA1c, serum creatinine levels or estimated glomerular filtration rate. However, C-peptide positive patients had higher post-transplant C-peptide levels and T2DM phenotype (overweight or obese, hyperlipidemia, family history of diabetes, progressive insulin resistance)^[63]. The authors concluded that positive C-peptide “should not be used exclusively to determine candidacy for SPK transplant”^[62].

Light *et al*^[64] performed a retrospective analysis of 173 SPK recipients, of whom 66.5% had negligible C-peptide (“C-peptide negative”, < 0.8 ng/mL). The elevated C-peptide group (“C-peptide positive”, ≥ 0.8 ng/mL) tended to have T2DM phenotype and C-peptide levels > 5 ng/mL. In long-term follow-up (up to 20 years), “C-peptide negative” patients had significantly improved survival ($P = 0.019$); “C-peptide positive” recipients showed a trend to better survival ($P = 0.069$). Similar to Stratta *et al*^[62], this study indicates that “C-peptide positive” (T2DM phenotype) patients can have favorable outcomes post SPK transplant^[64]. A more recent by Shin *et al*^[65] compared 5-year outcomes among 151 T1DM and 42 T2DM pancreas transplant recipients. There was no difference in hemoglobin A1c levels, fasting insulin levels, homeostasis model assessment of insulin resistance or the insulinogenic index between the groups. Notably, insulin resistance decreased between both groups, even though T2DM recipients kept significantly higher C-peptide levels^[65].

The overweight and obese T1DM recipient

C-peptide positive or not, overweight (BMI 25-30 kg/m²) and obese (BMI > 30 kg/m²) pancreas transplant candidates are becoming increasingly common^[34]; possibly reflecting the global obesity epidemic^[66]. T1DM patients may be overweight or obese and still benefit from pancreas transplant. That being said, such patients are not immune to the general obesity-linked surgical risk^[68,71]. On a large scale SRTTR analysis of 21000 pancreas transplant recipients, Bedat *et al*^[72] showed that overweight and

Table 3 Studies on Simultaneous pancreas and kidney transplant outcomes of C-peptide positive vs C-peptide negative recipients

| First author, yr | Country | No. patients | Study period | C-peptide positive (%) | BMI (kg/m ²) Mean (SD) | Follow-up (yr) | Outcomes | Conclusion |
|---|-------------------|--------------|--------------|------------------------|--|----------------|--|--|
| Chakkeria <i>et al</i> ^[61] , 2010 | United States | 80 | 2003-2008 | ^a 15 | T1DM 24.8 (4.2); T2DM 27 (3) | 1 | No difference in graft (kidney and pancreas) or patient survival. | SPK should be considered in selected patients with T2DM and ESRD. C-peptide measurements for ESRD patients can be misleading. |
| Light <i>et al</i> ^[64] , 2013 | United States | 173 | 1989-2008 | ^c 33.5 | T2DM 26.1 (ns) ^d ; T1DM 22.5 (ns) ^d (P < 0.0001) | 20 | T2DM were older at diabetes diagnosis, older at transplant, and heavier pre- and post-transplant, and had better graft survival. T1DM had better patient survival | There was a difference in patient but not graft survival in 20 yr follow-up. |
| Stratta <i>et al</i> ^[62] , 2015 | United States | 162 | 2001-2013 | ^b 18.5 | T2DM 26.1 (3.3); T1DM 24.4 (3.2) | 5.6 (median) | No difference in patient and graft survival or surgical complications, rejections, serum creatinine, HbA1c, eGFR, C-peptide and weight gain were higher in the C-peptide positive group. | C-peptide “positive” patients appear to have a T2DM phenotype. Outcomes were similar between the two groups, suggesting that C-peptide should not be used exclusively when assessing for SPK transplant candidacy. |
| Shin <i>et al</i> ^[65] , 2017 | Republic of Korea | 217 | 2004-2015 | ^e ns | T2DM 38 (9); T1DM 18 (7) | 5 | Similar post-operative HbA1c (< 6%), fasting insulin, HOMA of insulin resistance, and insulinogenic index. Higher post-transplant C-peptide in T2DM recipients. | No significant difference in insulin resistance or β -cell function in 5 yr. |

^aT2DM definition: C-peptide presence, negative glutamic acid decarboxylase antibody, no diabetic ketoacidosis, use of oral hypoglycemics;

^bC-peptide “positive” (T2DM) = C-peptide \geq 2.0 ng/mL; C-peptide “negative” = C-peptide < 2.0 ng/mL;

^cPatients with undetectable C-peptide (< 0.8 ng/mL) were considered T1DM; patients with detectable C-peptide (> 0.8 ng/mL) were considered T2DM;

^dSD not stated;

^ePatients were classified as T1DM and T2DM, based upon the American Diabetes Association and the World Health Organization definitions of T2DM. As such, there were 151 T1DM [C-peptide 0.92 (SD = 0.58) ng/mL] and 42 T2DM [C-peptide 3.49 (SD = 3.95) ng/mL] patients. T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; ESRD: End-stage renal disease; eGFR: Estimated glomerular filtration rate; HbA1c: Glycosylated hemoglobin A1; SPK: Simultaneous kidney-pancreas transplant; ns: Not stated; HOMA: Homeostasis model assessment.

obesity are independent predictors of increased early mortality and graft loss, and obesity is associated with inferior long-term graft survival. In an earlier series, Sampaio *et al*^[73] reached similar conclusions.

Is there a role for bariatric surgery?

Bariatric and metabolic surgery is an established method of treatment of T2DM and metabolic syndrome^[74-76]. It is yet to be clarified whether a metabolic procedure, may it

be sleeve gastrectomy or a more complex restrictive and malabsorptive procedure such as Roux-en-Y gastric bypass, would provide survival benefit on a patient with negligible insulin production.

T2DM patients with BMI ≥ 32 kg/m², currently non-eligible for pancreas transplant in most United States centers, should be considered for metabolic surgery^[74-76]; if their post-bariatric surgery BMI drops to ≤ 30 kg/m² but they remain insulin-dependent, suffer from brittle diabetes, insulin intolerance and/or hypoglycemia unawareness, they may be channeled towards pancreas transplant.

T1DM patients with BMI > 28 kg/m², who are currently considered poor pancreas transplant candidates, may be reconsidered for transplant after adequate weight loss. Excess weight loss prior to pancreas transplant may improve pancreatic graft survival^[72]; plus, it will probably temper the obesity-related cardiovascular morbidity and mortality^[77]; even though its benefit on T1DM population post-pancreas transplant is yet to be described.

The chronic pancreatitis patient: Islet autotransplant after total pancreatectomy

Total pancreatectomy without pancreatic endocrine function replacement will result in brittle diabetes and life-threatening hypoglycemia due to vanished pancreatic α - and β -cell function. According to 2014 PancreasFest consensus and 2015 National Institute of Diabetes and Digestive and Kidney Diseases, TPIAT is a potential treatment option for selected patients with impaired quality of life due to severe painful chronic pancreatitis, where conservative measures have failed^[19,20]. TPIAT should not be performed in patients with active alcoholism or illicit substance use, T1DM, pancreatogenic diabetes, portal vein thrombosis, portal hypertension, significant liver disease, severe cardiopulmonary disease, pancreatic cancer, untreated or uncontrolled psychiatric disorder or history of poor compliance^[78]. A retrospective review of 75 children undergoing TPIAT showed sustained pain relief and improved quality of life, whereas beta-cell function was dependent on islet yield^[78]. Fan *et al*^[79] from Johns Hopkins University recently published a smaller series of 32 patients who underwent laparoscopic TPIAT, resulting in sustained pain relief, earlier recovery and variable insulin dependence. There is vast potential for future research in this emerging field.

DISCUSSION

Pancreas transplant is a potentially curative option for T1DM, re-establishing euglycemia and, therefore, independence from the need of external insulin administration and glucose monitoring. The Heidelberg group analysis of > 20 years outcomes based on International Collaborative Transplant Study data, demonstrated that pancreas transplant benefits become obvious after 10 years, at which time it confers survival benefit superior to LDKT among uremic T1DM patients^[31,32]. The group also reported diminished death rates from cardiovascular events beyond 10 years^[31,32]. Despite these obvious benefits, the transplant community maintains a rather conservative approach. Donor pancreata remain underutilized^[8]; the United States pancreatic discard rates are close to 30%^[47]. DCD pancreata are seldom procured^[40]; steatotic pancreatic allografts are commonly discarded; and obese donors are commonly considered poor pancreatic donation candidates^[35,36]. European study groups showed that procurement professionalization is associated with increased pancreatic allograft utilization, and that high-volume pancreas transplant centers are associated with superior outcomes (Table 2)^[49-53]. United Kingdom and OPTN registry analyses demonstrated that DCD and DBD SPKs could have indistinguishable outcomes (Table 1)^[41,43-46]. OPTN registry analysis indicated that heavier donor (BMI 30-35 kg/m²) pancreata might provide comparable outcomes^[37]. On the recipient end, pancreas transplant has been shown to be beneficial to selected C-peptide positive patients (Table 3)^[64-66].

This study has several limitations. It is a narrative review; as such, it has strong vulnerability to article selection bias; and databases have not been searched in a systemic way. There is limited number of studies exploring the various topics discussed, with series of publications often reported by the same institutions. Another inherent limitation is that most studies included were prospective or retrospective OPTN/UNOS, United Kingdom or DTF cohort reports or case series, which were founded on skewed datasets, since surgeons had already balanced donor-recipient risk at the time of organ/recipient selection and transplant.

CONCLUSION

Pancreas donors remain underutilized. DCD and obese donors should be considered for pancreas donation; the pancreas procurement process should be audited, standardized and optimized. Selected T2DM patients should be considered for pancreas transplant.

More very long-term follow-up studies should be performed in order to delineate the long-term cardiovascular and quality-of-life benefits of pancreas transplant; the results of which might eventually ascertain the pancreas transplant role in the armamentarium of definitive diabetes treatment.

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