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Outcomes of pancreas transplantation in older diabetic patients

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ABSTRACT

Objective Improvement in insulin alternatives is leading to a delayed presentation of microvascular and macrovascular complications of diabetes. The objective of this study was to evaluate the long-term outcomes of older (≥50 years) diabetic patients who receive a pancreas transplantation (PT).

Research design and methods We retrospectively evaluated all 338 PTs performed at our center between 2000 and 2016 (mean follow-up 9.4±4.9 years). Recipient and graft survivals were estimated for up to 10 years after PT. Major adverse cardiovascular events (MACEs) before and after PT were included in the analysis.

Results Thirty-nine patients (12%) were ≥50 years old (52.7±2.3 years) at the day of PT, of which 29 received a simultaneous pancreas–kidney transplantation (SPK) and 10 a pancreas after kidney transplantation (PAK). SPK recipients were first transplants, whereas in the PAK up to 50% were pancreas re-transplantations. Recipient and pancreas graft survivals at 10 years were similar between the group <50 years old and the older group for both SPK and PAK (log-rank p>0.05). The prevalence of MACE prior to PT was similar between both groups (31% vs 29%). Following PT, older recipients presented inferior post-transplant MACE-free survival. In a multivariate regression model, diabetes vintage (HR 1.054, p=0.03) and pre-transplantation MACE (HR 1.98, p=0.011), but not recipient age (HR 1.45, p=0.339), were associated with post-transplant MACE.

Conclusions Long-term survival of older pancreas transplant recipients are similar to younger counterparts. Diabetes vintage, but not age, increased the risk of post-transplantation MACE. These results suggest pancreas transplantation is a valuable treatment alternative to older diabetic patients.

Significance of this study

What is already known about this subject?

- During the last years, there has been an increase in the mean age of the patients included in the pancreas transplantation waiting list.
- Recent studies suggest that age is not associated with worse patient nor graft survivals after pancreas transplantation.
- Several studies suggest that age is an independent risk factor for major adverse cardiovascular events after pancreas transplantation.

What are the new findings?

- In older recipients (≥50 years old), 10-year patient and graft survivals after pancreas transplantation are similar to younger recipients (<50 years old).
- Incidence of fatal major adverse cardiovascular events after pancreas transplantation is not increased in older pancreas transplant recipients.
- Age per se is not associated with an increased risk of post-transplant major adverse cardiovascular events.

How might these results change the focus of research or clinical practice?

- Pancreas transplantation is a valuable treatment alternative to recipients ≥50 years old since the outcomes of judicious selected older recipients are similar to their younger counterparts.

INTRODUCTION

Diabetes mellitus is a highly prevalent disease worldwide, associated with multiple microvascular and macrovascular complications that compromise patient's survival. Within the therapeutic arsenal in diabetes, pancreas transplantation (PT), either pancreas transplantation alone (PTA), pancreas after kidney transplantation (PAK), and simultaneous pancreas–kidney transplantation (SPK), have proved to be therapeutic alternatives able to achieve euglycemia without exogenous insulin requirements and providing a significant improvement in patient survival at short-term, medium-term, and long-term follow-up.[1 2]

During the last years, there have been important therapeutic advances in diabetes mellitus care. These have led to a better control of cardiovascular risk factors in these patients, thus delaying development of diabetes-derived microvascular and macrovascular complications (including a delayed progression to end-stage kidney disease, ESKD).[3] This phenomenon justifies the observed increase in the mean age of the patients referred for assessment for pancreas transplantation and, consequently, the mean

age increase of the patients included in the pancreas transplantation waiting list.[2 4]

Due to the significant complexity and surgical risks associated with pancreas transplantation, as well as the marked cardiovascular burden of patients with diabetes and their infection risk, this therapeutic option is often reserved for younger patients, being age (>45–50 years) an exclusion criteria in many centers worldwide.[1 5 6] However, the information available about the impact on survival (both of recipient and kidney and pancreatic grafts) of PT in elderly patients is limited. Recent studies suggest that age is not associated with worse patient nor graft survivals after PT, probably related (at least in part) with a significant improvement in surgical techniques, immunosuppressive schemes, and post-PT care.[1 3 6–9]

Another aspect to consider is the incidence of major adverse cardiovascular events (MACEs) after PT and its relationship with the age of the recipient. Several studies suggest that the incidence of MACE after PT increases with the age of the recipient, being age an independent risk factor for post-PT MACE.[3 10] However, most of these studies do not take into account certain factors inherent to older age, such as the diabetes vintage or the incidence of MACE prior to PT.

The aim of this study was to evaluate the impact of pancreas transplantation on the recipient, pancreatic, and kidney graft survivals, as well as the impact of the age on the rate of post-PT MACE in a population of pancreas recipients over 50 years old.

RESEARCH DESIGN AND METHODS

Study design

Following protocol approval by the ethics committee institutional review board, we conducted a single-center retrospective analysis including all pancreas transplants performed at our center from January 1, 2000 until December 31, 2016, including SPK and PAK. PTA and SPK re-transplantations were excluded from the analysis due to the small sample size (n=1 and n=3, respectively). Moreover, due to the small sample size and in order to avoid an excessive fragmentation of the PAK population, first PAK (n=23), pancreas re-transplantation (re-PT) following an SPK (n=28) and PAK (n=3) were considered as a single group for statistical analysis. Data were collected until December 31, 2017.

Both donor and recipient data were included, such as demographic, clinical, biochemical, and immunologic. Two donor pancreas scoring systems were included in the analysis—the Pre-Procurement Pancreas Allocation Suitability Score, which was calculated based on the original publication from Vinkers *et al*,[11] and Pancreas Donor Risk Index, according to the description of Axelrod *et al*.[12]

Patient population

Recipients with insulin-dependent diabetes (type 1 or selected type 2 patients) with ESKD stages 4–5D (estimated glomerular filtration rate (eGFR) <20 mL/min/1.73 m^2) received an SPK, and kidney transplant recipients with normal kidney graft function (eGFR >40 mL/min/1.73 m^2) a PAK. Pre-transplant workup included biochemical and hematological parameters, cardiologic evaluation, and CT scan of splanchnic and iliac vessels. Immunological workup included complement dependent cytotoxicity and panel-reactive antibodies for patients with low immunological risk (absence of previous blood transfusions or solid organ transplant). Solid-phase Luminex screening was performed for those with previous sensitization episodes, and solid-phase single-bead antigen was performed in the presence of a positive class I and/or II Luminex screening.

Survival definition

Patient survival was defined as last day of follow-up, date of death with a functioning pancreas graft, or at 90 days following failure of pancreas graft. Pancreas graft failure was defined as any of the following: (1) graft removal, (2) C-peptide <1 ng/mL, (3) total daily insulin need >0.5 U/kg, or (4) patient death. Pancreas early graft failure (EGF) was defined as any pancreas graft failure during the first 90 days following pancreas transplantation.

Kidney graft failure was defined as any of the following: (1) return to dialysis, (2) re-transplantation, or (3) patient death. Kidney delayed graft function was defined as the need for at least one session of hemodialysis during the first week following SPK.

Major adverse cardiovascular events

MACEs were computed based on digital data, and separated whether having occurred prior to or following pancreas transplantation. Cardiac events included ischemic cardiac disease (clinical or subclinical), documented on a stress test or demonstrated by coronariography, with or without revascularization. Cerebrovascular events were recorded according to the presence of ischemic or hemorrhagic episodes. Peripheral vascular events were assumed as the need for peripheral revascularization or amputation (including digit amputation).

Surgical technique

All pancreas transplants procedures at our center since 1998 were performed with enteric anastomosis. Until 2016, a duodeno-jejunal anastomosis with intraperitoneal position was used, and from June 2016 onwards a retroperitoneal with duodeno-duodenal anastomosis was used. Systemic venous drainage was performed through anastomosis between graft's portal vein to the recipient's inferior vena cava. For the arterial anastomosis, in the back table superior mesenteric artery was end-to-end anastomosed to splenic artery. In the current era, a Y graft is used. Arterial anastomosis is performed to the recipient common iliac artery or directly to the aorta. Both procedures have been previously described.[13–15]

Anticoagulation and immunosuppression

Anticoagulation was standard in pancreas transplantation, regardless of being PAK or SPK. Our protocol

included subcutaneous enoxaparin 20 mg twice daily starting 8 hours post-surgery and was maintained until patient discharge (in the absence of thrombotic/hemorrhagic complications), and acetylsalicylic acid 50 mg/day starting at 12 hours post-surgery until discharge, when it is increased up to 100 mg/day.

Induction immunosuppression therapy was used in all patients. In SPK, two doses of anti-IL2 monoclonal antibody (basiliximab) of 20 mg at day 0 and at day +4 after surgery was used as standard therapy until July 2013, and thereafter replaced by rabbit anti-human lymphocyte polyclonal antibodies (either Thymoglobulin 1.25 mg/kg/day or ATG 2.5 mg/kg/day) for four consecutive days. In PAK, these doses were extended to seven consecutive days.

Maintenance immunosuppression protocol was based on triple therapy with calcineurin inhibitor (ciclosporin A until 2005, and thereafter tacrolimus), mycophenolate, and steroids—methylprednisolone in the immediate post-transplant period, followed by oral prednisone. Prednisone was withdrawn in low immunological risk SPK recipients before month 6, in the absence of any immunological event during the first 3 months.

Statistical analysis

For continuous variables, a Kolmogorov-Smirnov test was used to determine normality. Parametric variables are described as mean (SD), and non-parametric as median (IQR), and the corresponding tests used (t-test, ANOVA, Kruskal-Wallis). Kaplan-Meier was used to estimate unadjusted patient and graft survivals and compared using log-rank test. Binominal logistic regression was used to calculate OR, and Cox proportional regression performed to estimate grafts' and MACEs' hazards. Statistical analysis was performed using SPSS (V.22) software, with all tests two-tailed and significance considered if p value <0.05.

RESULTS

During the study period, 338 pancreas transplants were performed, with a mean follow-up of 9.4±4.9 years. A total of 39 (12%) PTs were performed in recipients ≥50 years old (range 50.1–59.3). As expected, there were significant differences in age (38.7±6.2 vs 52.7±2.3 years in the group of <50 vs ≥50 years, respectively; p<0.0001) and duration of type 1 diabetes mellitus (25.2±7.7 vs 34.2±10 years in the group of <50 vs ≥50 years, respectively; p<0.0001). There were no significant differences between both age groups in terms of dialysis type or vintage, pancreas transplantation type, donor characteristics, immunological sensitization, nor immunosuppressive regimen. The majority of pancreas transplants (69%) in the group ≥50 years old were performed in the most recent era (between 2008 and 2016, p<0.05). The prevalence of MACE prior to pancreas transplantation was similar between both age groups (29% vs 33% in the group of <50 vs ≥50 years, respectively; p>0.05). Prevalence of ischemic heart disease prior to pancreas transplantation was of 8.3% (25 episodes) in the younger group, of which 7 (28%) and 4 (16%) underwent percutaneous and surgical revascularization, respectively. In the older group, pre-transplant ischemic heart disease prevalence was of 5.1% (two episodes) and only one was percutaneously revascularized. Table 1 summarizes the demographic characteristics of donors and recipients according to recipient age. Online supplementary table S1 summarizes these data according to recipient age and pancreas transplantation type (SPK or PAK). Due to differences in recipients between SPK and PAK, results were analyzed separately.

Simultaneous pancreas–kidney transplantation

Recipient survival estimates were similar between both groups, with survival at 12 months, 5 years, and 10 years of 98.4%, 95.8%, and 95.8% for the group <50 years, and for those ≥50 years old of 96.6%, 89.3%, and 89.3%, respectively (p=0.097) (figure 1A). There were no significant differences between both groups for cause of death (p=0.58) (table 2). Nonetheless, infection was the main cause of death in the group <50 years (seven cases, 43%), being respiratory and abdominal infections the most frequent with four cases for each one; while in the group ≥50 years, it was cardiovascular disease (two cases, 50%).

Death-censored pancreas graft survival at 12 months, 5 years, and 10 years was of 89%, 81.9%, and 76%, respectively, for the group <50 years old and of 89.7% for the same three time points in the older group (p=0.24) (figure 1B).

The most frequent cause of pancreas graft loss in the group <50 years old was acute/chronic rejection (41.4%), whereas in the group ≥50 years old (excluding deaths with a functioning graft) were surgical complications and acute/chronic rejection (28.6% for both causes) (see online supplementary table S2). EGF was similar between the younger group (9.4%) and the older group (6.8%) (p=0.48).

Regarding post-transplant complications, no major differences were observed between the two groups as to incidence of surgical complications or reintervention rates. Time from pancreas transplantation to patient discharge was also similar (see online supplementary table S3).

The overall incidence of acute rejection was not different between the two groups (20.5% vs 25.6% in younger vs older recipients, respectively; p=0.288). Estimated rejection-free graft survival was similar between both groups (log-rank p=0.485), with a median to first rejection of 4.4 (1.3–15) months in younger recipients compared with 8.2 (1.7–48.7) months in older ones (p=0.411).

In those with a functioning graft, HbA1c (5.3±1.2 vs 5.2±0.9; p=0.54) and C-peptide (2.5 (2.0–3.7) vs 2.2 (1.8–3.2); p=0.24) was no different between young and older recipients, respectively, at 12 months (see online supplementary table S3).

Table 1 Recipient and donor demographics according to recipient age

	<50 years (n=299)	≥50 years (n=39)	P value
Recipient			
Gender (female; n, %)	111 (37)	11 (28)	0.38
Age (years; mean±SD)	38.7±6.2	52.7±2.3	<0.0001
BMI (kg/m^2; mean±SD)	23.2±3.8	25.1±4.0	0.01
Diabetes mellitus vintage (years; mean±SD)	25.2±7.7	34.2±10	<0.0001
Diabetes mellitus type (n, %)			0.04
Type 1	298 (99.7)	37 (95)	
Other types*	1 (0.3)	2 (5)	
HbA1C (pre-transplant, %; mean±SD)	7.8±1.9	7.9±1.7	0.65
Glucose (pre-transplant, mg/dL; mean±SD)	178±54	179±48	0.87
C-Peptide (pre-transplant, ng/mL; median (IQR))	0.15 (0.1–0.2)	0.16 (0.1–0.2)	0.77
Anti-GAD (pre-transplant, U/mL; median (IQR))	0.3 (0.1–3.5)	0.2 (0.1–1.8)	0.42
Hypertension (yes; n, %)	131 (43)	17 (44)	0.97
LDL (at transplant, mg/dL; mean±SD)	100.48±37.8	99.35±37.4	0.90
Total cholesterol (at transplant, mg/dL; mean±SD)	168.79±48.7	166.84±48.6	0.81
Antihyperlipidemic treatment (at transplant, yes; n, %)	98 (32)	14 (36)	0.66
Smoking habit (at transplant, yes; n, %)			<0.0001
Current smoker	65 (22)	2 (5)	
Ex-smoker	38 (13)	14 (36)	
Dialysis type (n, %)			0.69
Pre-emptive	26 (8)	2 (5)	
Hemodialysis	157 (53)	17 (44)	
Peritoneal dialysis	72 (24)	10 (28)	
Dialysis vintage (months; mean±SD)	31.7±21.9	29.5±19.6	0.54
MACE pre-transplant (any; yes; n, %)	87 (29)	13 (33)	0.58
Transplant type (n, %)			0.34
SPK	255 (84)	29 (74)	
PAK	18 (5.9)	5 (13)	
Re-PT	26 (9)	5 (13)	
Pancreas transplant era (n, %)			0.012
2000–2007	152 (50)	12 (31)	
2008–2016	147 (49)	27 (69)	
Waiting list vintage (months; mean±SD)	14.6±11.7	16.4±13.4	0.38
Sensitization pre-transplant (n, %)	44 (15)	9 (23)	0.82
HLA mismatches (mean±SD)	4.7±1.1	4.7±1.4	0.94
Immunosuppression (n, %)			0.98
Thymoglobulin	142 (47)	18 (47)	
Basiliximab	128 (43)	17 (42)	
OKT3	29 (10)	4 (11)	
Prednisone withdrawal (n, %)	97 (32)	7 (18)	0.06
CMV donor/recipient status for IgG (n, %)			0.39
Negative/negative	19 (6)	0 (0)	
Negative/positive	70 (23)	8 (21)	
Positive/negative	32 (11)	5 (13)	

Continued

Table 1 Continued

	<50 years (n=299)	≥50 years (n=39)	P value
Positive/positive	113 (38)	16 (41)	
Unknown	65 (22)	10 (25)	
Donor			
Age (years; mean±SD)	31.1±10.8	28.7±9.9	0.18
BMI (kg/m^2; mean±SD)	23.5±2.9	23.5±3.1	0.99
P-PASS (mean±SD)	15.9±2.6	15.4±2.9	0.37
PDRI (mean±SD)	1.28±0.39	1.19±0.41	0.32
CIT (h; mean±SD)	10.5±3.0	10.0±2.5	0.31

*All cases of other types of diabetes mellitus were due to necrohemorrhagic pancreatitis.
anti-GAD, glutamic acid decarboxylase antibodies; BMI, body mass index; CIT, cold ischemia time; CMV, cytomegalovirus; HLA, human leukocyte antigen; LDL, low-density lipoprotein; MACE, major adverse cardiovascular event; PAK, pancreas after kidney transplantation; PDRI, Pancreas Donor Risk Index; P-PASS, Pre-Procurement Pancreas Allocation Suitability Score; PTA, pancreas transplantation alone; Re-PT, re-pancreas transplantation; SPK, simultaneous pancreas–kidney transplantation.

In the case of kidney graft, the survival did not differ significantly between the two groups analyzed. Death-censored kidney-graft survival was for the group <50 years old at 12 months, 5 years, and 10 years of 98.0%, 93.1%, and 87.7%, and for the group ≥50 years old was of 100% at 12 months and 5 years, respectively, and 85.7% at 10

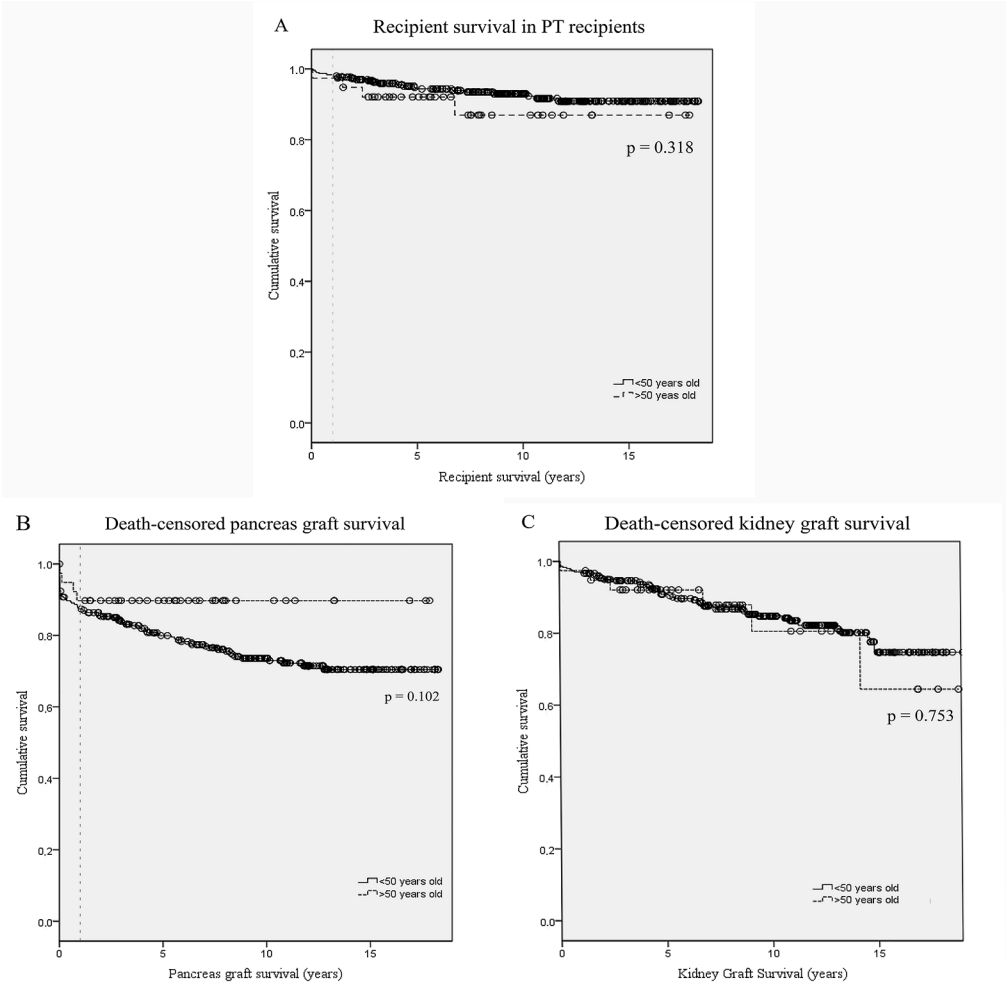

Figure 1 (A) Recipient survival in SPK recipients. (B) Death-censored pancreas graft survival considering only SPK recipients. (C) Death-censored kidney graft survival considering only SPK recipients. SPK, simultaneous pancreas–kidney transplantation; white circles—censored values.

Table 2 Causes of death in both age groups

	SPK			PAK		
	<50 years old n (%)	≥50 years old n (%)	P value	<50 years old n (%)	≥50 years old n (%)	P value
Cardiovascular disease	3 (19)	2 (50)	0.58	0 (0)	0 (0)	1
Infection	7 (44)	1 (25)		3 (50)	0 (0)	
Neoplasia	2 (12)	1 (25)		0 (0)	0 (0)	
Gastrointestinal hemorrhage	0 (0)	0 (0)		2 (33)	0 (0)	
Other causes	2 (12)	0 (0)		0 (0)	0 (0)	
Unknown	2 (12)	0 (0)		1 (17)	0 (0)	

PAK, pancreas after kidney transplantation; SPK, simultaneous pancreas–kidney transplantation.

years (p=0.69) (figure 1C). Delayed graft function of kidney graft was similar between both groups (9.1% and 10.3% in younger and older group, respectively, p=0.51).

The overall incidence of MACE after pancreas transplantation was superior in the older group (31% vs 20% in the younger group), though it failed to reach statistical significance (p=0.29). Incidence of ischemic heart disease was 9% (22 episodes) for the younger group, of which 8 (36%) and 2 (9%) were percutaneously and surgically revascularized. For the older group, ischemic heart disease incidence was of 3% (1 episode, non-revascularized). The most frequent MACE in both groups was peripheral vascular disease (10% and 14% for the group <50 and ≥50 years, respectively) (see online supplementary table S3).

The estimated MACE-free survival was significantly lower for the group ≥50 years old (92.9%, 70.3%, and 70.3% at 12 months, 5 years, and 10 years, respectively, compared with 96.5%, 91.1%, and 78% for the same periods in the younger group; p=0.015) (figure 2A).

On the univariate Cox regression analysis, age ≥50 years was a risk factor for post-transplant MACE (HR 2.35, 95% CI 1.16 to 4.79, p=0.019) (figure 2B). However, in a multivariate Cox regression model, recipient age ≥50 years loses its significance as an independent risk factor for the development of post-transplant MACE (HR 1.45, 95% CI 0.68 to 3.13, p=0.339). Importantly, diabetes vintage (HR 1.054, 95% CI 1.018 to 1.091, p=0.03) and having had a MACE prior to PT (HR 1.98, 95% CI 1.17 to 3.34, p=0.011) significantly increases the risk. A failed pancreas graft during the first 12 months appeared not to be a risk (p=0.121) (see online supplementary table S4).

Pancreas after kidney transplantation

Of the 54 recipients included in this group, 23 patients (43%) were recipients of a first PAK, of which 15 had previously received a living donor kidney transplantation (LDKT), and 8 a deceased donor kidney transplantation. The remaining 31 patients (57%) were recipients of a re-PT, of which 28 (90%) had previously received a SPK and 3 (10%) a LDKT.

Recipient survival estimates were similar between both groups, with survival at 12 months, 5 years, and 10 years of 97.8%, 85.3%, and 85.3%, respectively, for the younger group and of 100% for the three moments analyzed for the older group (p=0.249) (see online supplementary

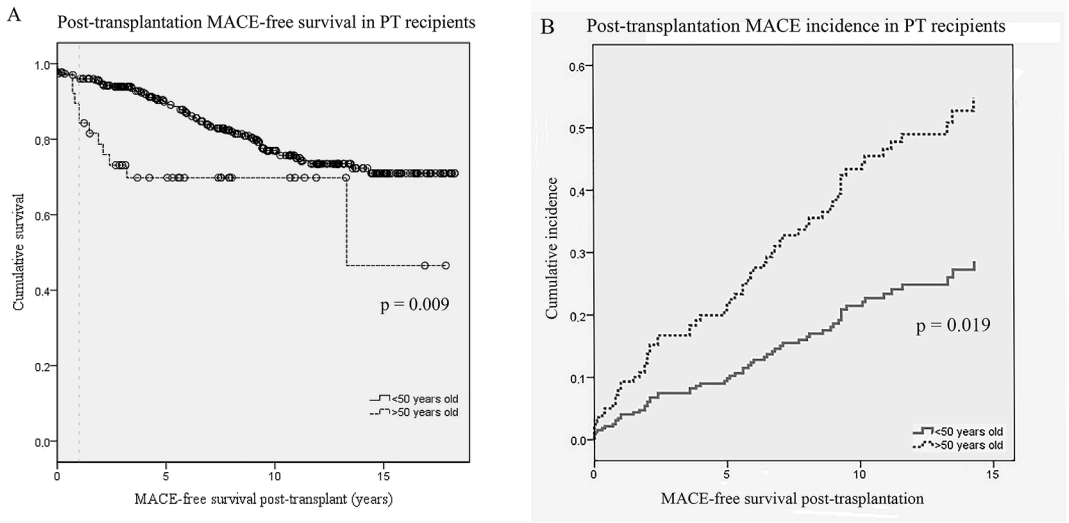

Figure 2 (A) Kaplan-Meier estimates for MACE-free survival in SPK recipients. (B) Cox regression analysis for the incidence of MACE after PT. MACE, major adverse cardiovascular event; PT, pancreas transplantation; SPK, simultaneous pancreas–kidney transplantation. White circles—censored values.

figure S1A). In the younger group, the major cause of death was infection (three cases, 50%). There were neither differences between both age groups according to pancreas transplant modality (first PAK or re-PT, log-rank p=0.43 and p=0.40, respectively).

Death-censored pancreas graft survival at 12 months, 5 years, and 10 years was of 77.6%, 67.8%, and 57.8%, respectively, for the younger groups and for the older group of 90% for the three moments analyzed (p=0.118) (see online supplementary figure S1B), irrespective of being a first PAK (log-rank p=0.53) or a re-PT (log-rank p=0.12). The incidence of graft thrombosis was numerically higher in the younger group (40% vs 20% in older group; p=0.62) (see online supplementary table S3), with a higher incidence of graft failure due to surgical complications (43% vs 0% in older group) (see online supplementary table S2).

Acute rejection incidence was similar between both groups (38% vs 40% in the younger and older groups, respectively; p=0.58). The median to the first rejection was of 4.2 months (IQR 1.3–15) for the younger group and of 6 months (IQR 0.4–30) to the older group (p=0.96), with a rejection-free graft survival at 12 months of 72% and 68% for each group, respectively (log-rank p=0.89).

The overall MACE incidence pre-transplant was similar between both groups (36% and 30% in young and older groups, respectively; p=0.52) (see online supplementary table S1). The post-transplant MACE incidence was higher for the older group (30% vs 22% in younger group; p=0.44) and presented sooner (median to first MACE of 0.7 months (IQR 0.1–3.2) for the older group vs 4.2 months (IQR 0.8–4.6) for the younger one; p=0.11), though it failed to reach statistical significance (see online supplementary table S3). The MACE-free survival at 10 years was similar between both groups (70% vs 67% in younger and older groups, respectively; log-rank p=0.45).

DISCUSSION

In the study herein presented, we analyze the outcomes of older diabetic patients who receive a pancreas transplantation. In summary, we demonstrate that patient and graft survival up to 10 years after transplantation was similar between recipients older than 50 years compared with the rest, regardless of being an SPK or a PAK. An overall similar incidence on MACEs following PT was observed between both groups. Nonetheless, in older recipients they tended to present sooner after PT, leading to an inferior estimated MACE-free survival in this group, particularly in the SPK group. Diabetes vintage and, most importantly, the presence of a MACE prior to transplantation were the most relevant risk factors for MACE following PT. Of relevance, age was not independently associated with an increased risk of post-transplantation MACE.

In the former two decades, improvement in glycemic control by the development of novel exogenous insulin formulations and glycemic monitoring apparatus has led to an overall reduction in the incidence of microvascular and macrovascular complications of diabetes.[3] As a direct consequence, mean age of patients at inclusion on the waiting list for pancreas transplantation has been rising, with an increase from 37 to 40 years old in Spain between 2006 and 2018.[4] In the USA, 27% of recipients waitlisted in 2017 were 50 years old or older, and 51 (3%) were older than 60.[2] The PT recipient age impact on patient survival and pancreatic graft (and kidney, in SPK modality) is a controversial aspect that, sometimes, limits per se the candidate selection for a pancreas transplantation[1 3 5 6]: in 1998, Freise *et al*[6] reported that SPK recipients older than 49 years had a higher mortality than those younger (30% vs 5.3% at 1 year, respectively). Surprisingly, none of the deaths in the group of patients older than 49 years were due to cardiovascular disease—although the mean follow-up was of only 12 months after transplantation. Moreover, kidney and pancreatic 1-year graft survival were also lower in the older group. However, more recently, Scalea *et al*[3] demonstrated a comparable survival (for the patient, kidney, and pancreatic graft) between the older groups (45–54 and ≥55 years) with the younger ones. Accordingly with these results, in our cohort we also observed non-inferior patient nor grafts survivals' in the older recipients (≥50 years). The results from both cohorts suggest that age itself is not associated with poorer outcomes after PT. As stated by Sutherland *et al*,[1] the improvement in post-transplant outcomes in the most recent eras (especially in SPK), linked to advances in surgical techniques, immunosuppressive treatment, and post-transplant care, should be taken into account when analyzing the results. These improvements have likely led to less stringent selection of the recipient for PT. In our cohort, we observed that most patients in the older group underwent transplantation in the most recent years (2008–2016), which may justify (at least in part) the absence in the rate of postsurgical complications and of patient survival.

In terms of cardiovascular disease, the DCCT/EDIC trial was one of the major studies to demonstrate the relevance of a strict glycemic control on long-term cardiovascular outcomes.[16 17] In the DCCT, a mean HbA1c of 7.2% in the intensive treatment group reduced the early stages of microvascular complications by 35%–76% compared with the conventional treatment group (mean HbA1c 9.1%).[18] Nevertheless, one of the most important adverse events which was most frequently reported in the intensive care group was hypoglycemia.[18] In this sense, PT is an alternative treatment to selected patients with diabetes which is able to achieve euglycemia with a low risk of hypoglycemia and that has demonstrated to improve patient survival[19 20] and reduce cardiovascular-related death compared with kidney transplant alone.[21] The observational study phase (EDIC study) following the DCCT demonstrated major long-term benefits for the intensive treatment group of the DCCT compared with controls, particularly regarding microvascular and macrovascular complications, including MACE.[16–18 22–25]

In general population, cardiovascular disease is directly correlated with age,[21] and it has been previously reported that older PT recipients also presented an increased incidence of MACE compared with younger recipients, with and incidence up to 65% on the need of cardiac catheterization in those older than 55 years old compared with 32% under 34.[3] In this study we have similar results, with older recipients presenting lower MACE-free survival and a cumulative MACE incidence of up to 31% at 10 years. Most importantly, despite age being associated with an increased risk of post-transplant MACE in the univariable, in a multivariate regression model, diabetes vintage and pre-transplant MACE, but not age, were found to be the only variables independently associated with an increased risk for MACE following PT, with pre-transplant MACE almost doubling the risk to present a new MACE after PT.

One of the most plausible explanations is the presence of metabolic memory in patients with long-lasting diabetes vintage or irregular glycemic control, which can be translated as the presence of irreversible cellular and tissue changes derived from prior poor metabolic control which eventually lead to secondary complications of diabetes.[26–28] The EDIC trial demonstrated that despite a similar metabolic control in the subsequent years to the DCCT trial, patients from the conventional control arm remained at a higher risk for cardiovascular disease compared with those from the intensive treatment arm.[16 17] The ability to reduce the metabolic fingerprint is the most accepted explanation to the improvement in patient survival in recipients of pancreas transplants who function for at least 12 months, compared with those whose pancreas did not last as long.[20 21] The results presented in this study re-enforce the ability of PT to avoid diabetes-associated complications and to improve long-term outcomes in patients with diabetes, regardless of the age, and shift the focus toward a careful recipient selection and thorough cardiovascular evaluation prior to transplantation, particularly in those with a MACE prior to transplantation.

The authors acknowledge there are some pitfalls to this study that should prompt caution when extrapolating the results. This represents a retrospective cohort of patients accepted for transplantation, and therefore a positive selection bias of those assumed fit for and which would most likely benefit from the transplantation. Center policy for acceptance of older recipients was limited to those who were expected to benefit the most on the long term of a functioning pancreas graft, whereas presenting the lowest short-term surgical risks, based on clinical evaluation prior to transplantation. The study is retrospective and the analysis dependent of recorded data. Moreover, amputations were the most frequent identified MACE, and peripheral vascular disease is not the major cause of death in pancreas transplant recipients, but rather ischemic cardiac disease.[20 29] Also, due to the small cohort (n=39) of recipients ≥50 years old and the short follow-up (9.4 years), in an era where pancreas graft half-life is close to 10–15 years,[2] no extrapolation of results to longer periods can be performed. Finally, it must be taken into account the PAK group evaluated here is highly heterogenic (includes first PAK for kidney deceased and living donor, as well as pancreas re-transplantation from previous SPK). The conclusions withdrawn may be limited when extrapolating the results to the general population of PAK recipients.

Despite these limitations, the authors believe this study provides novel insights into the importance of metabolic memory on long-term outcomes of PT in older recipients, and it re-enforces previous results demonstrating good short-term and long-term outcomes regarding patient and graft survivals. In PAK, and despite the group heterogenicity, it highlights that either first PAK or pancreas re-transplantations are feasible and should be evaluated as an alternative to older diabetic recipients since patient and graft outcomes up to 10 years are fairly good.

As closing remarks, the present work demonstrates that pancreas transplant outcomes are independent from the recipient age. Older recipients presented similar patient and graft outcomes, despite an increased risk to present a non-fatal MACE—particularly in those with longer diabetes vintage and who had had a MACE prior to PT. Therefore, PT should not be limited solely on chronological age since novel therapeutic alternatives for patients with diabetes postpone the appearance of diabetic secondary complications, and the outcomes of judicious selected older recipients of a PT are similar to their younger counterparts.

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Contributors EM-M collected, analyzed, and interpreted the data and prepared the manuscript. AM-A collected the data. AP collected the data. MJR-B analyzed and interpreted the data. EE analyzed and interpreted the data. JF analyzed and interpreted the data. FD analyzed and interpreted the data. PV-A, collected, analyzed, and interpreted the data and prepared the manuscript. Statistical analysis was performed by PV-A with EM-M. There were no other contributions for this work but the authors'.

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