Title

Impact of Sarcopenia on Simultaneous Pancreas and Kidney Transplantation Outcomes: A Retrospective Observational Cohort Study

Journal

Transplantation Direct, 6(10)

ISSN

2373-8731

Authors

Meier, Raphael PH
Noguchi, Hiroshi
Kelly, Yvonne M
et al.

Publication Date

2020

DOI

10.1097/txd.0000000000001053

OPEN

Impact of Sarcopenia on Simultaneous Pancreas and Kidney Transplantation Outcomes: A Retrospective Observational Cohort Study

Raphael P.H. Meier, MD, PhD,[1,2] Hiroshi Noguchi, MD,[1,3] Yvonne M. Kelly, MD,[1] Minnie Sarwal, MD, PhD,[1] Giulia Conti, MSc,[1] Casey Ward, MD,[1] Ran Halleluyan, MD,[1] Mehdi Tavakol, MD,[1] Peter G. Stock, MD, PhD,[1] and Chris E. Freise, MD[1]

Background. Sarcopenia has been identified as a predictive variable for surgical outcomes. We hypothesized that sarcopenia could be a key measure to identify frail patients and potentially predict poorer outcomes among recipients of simultaneous pancreas and kidney (SPK) transplants. **Methods.** We estimated sarcopenia by measuring psoas muscle mass index (PMI). PMI was assessed on perioperative computed tomography (CT) scans of SPK recipients. **Results.** Of the 141 patients identified between 2010 and 2018, 107 had a CT scan available and were included in the study. The median follow-up was 4 years (range, 0.5–9.1 y). Twenty-three patients had a low PMI, and 84 patients had a normal PMI. Patient characteristics were similar between the 2 groups except for body mass index, which was significantly lower in low PMI group ($P<0.001$). Patient and kidney graft survival were not statistically different between groups ($P=0.851$ and $P=0.357$, respectively). A multivariate Cox regression analysis showed that patients with a low PMI were 6 times more likely to lose their pancreas allograft (hazard ratios, 5.4; 95% confidence intervals, 1.4-20.8; $P=0.015$). Three out of 6 patients lost their pancreas graft due to rejection in the low PMI group, compared with 1 out of 9 patients in the normal PMI group. Among low PMI patients who had a follow-up CT scan, 62.5% (5/8) of those with a functional pancreas graft either improved or resolved sarcopenia, whereas 75.0% (3/4) of those who lost their pancreas graft continued to lose muscle mass. **Conclusion.** Sarcopenia could represent one of the predictors of pancreas graft failure and should be evaluated and potentially optimized in SPK recipients.

(*Transplantation Direct* 2020;6: e610; doi: 10.1097/TXD.0000000000001053. Published online 25 November, 2020.)

INTRODUCTION

Simultaneous pancreas and kidney (SPK) transplantation remain the best curative option for patients with type 1 diabetes and select patients with type 2 diabetes with chronic kidney disease.[1] After patients overcome the initial 3–6 months posttransplantation, the outcomes are excellent: quality of life is restored, kidney graft function remains preserved thanks to a restored euglycemic state, and patient

Received 23 June 2020. Revision received 20 July 2020.

Accepted 22 July 2020.

[1] Division of Transplant Surgery, Department of Surgery, University of California San Francisco, San Francisco, CA.

[2] Department of Surgery, University of Maryland School of Medicine, Baltimore, MD.

[3] Department of Surgery and Oncology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

Yvonne Kelly was supported by the NIH T32 Training grant (Grant number 5 T32 AI 125222-04).

The authors declare no conflicts of interest.

R.P.H.M. and H.N. have contributed equally to this article as cofirst author.

R.P.H.M. and H.N. designed the study. R.P.H.M., H.N., Y.K., M.S., G.C., C.W., R.H., M.T., P.G.S., and C.E.F. collected the data. R.P.H.M., H.N., Y.K., M.T., P.G.S., and C.E.F. analyzed the data. R.P.H.M. and H.N. performed statistical analysis. R.P.H.M., H.N., Y.K., M.S., G.C., C.W., R.H., M.T., P.G.S., and C.E.F. interpreted the data and wrote the article. R.P.H.M., H.N., and C.E.F. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

Availability of data

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Correspondence: Chris E. Freise, MD, Division of Transplant Surgery, Department of Surgery, University of California San Francisco, 505 Parnassus Ave, San Francisco, 94143 CA. (Chris.Freise@ucsf.edu), or Raphael P. H. Meier, MD, PhD, Department of Surgery, University of Maryland School of Medicine, Baltimore, MD. (Raphael.Meier@unige.ch).

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001053

survival is significantly improved.[2,3] The reasons for pancreas graft loss are multifactorial, including technical and vascular complications, leak, pancreatitis, acute and chronic rejection, and recurrence of type 1 or 2 diabetes. In addition to the classic risk factors described for graft loss, including donor/recipient age and body mass index (BMI), cold ischemia time, and the type of immunosuppression,[4] there are few modifiable predictors of pancreas graft survival. In diabetic patients with end-stage renal disease, objective measures such as sarcopenia have gained popularity to predict functional reserve and risk of complications after transplant.[5-8] Sarcopenia is characterized by a progressive loss of skeletal muscle mass and can be estimated by measuring psoas muscle area on cross-sectional imaging.[9] It has been recognized as an important predictor of poor reserve and has been associated with complications, morbidity, and mortality after major surgery.[10-13] Fukuda et al analyzed the role of sarcopenia in 41 SPK recipients and reported a nonsignificant trend associating low psoas muscle mass index (PMI) and pancreas graft survival.[6] They did, however, demonstrate a significant association between skeletal muscle quality (an alternative measure of sarcopenia) and both pancreas graft survival and postoperative complications. On the contrary, another study suggested that a low PMI might be protective; however, the numbers were very small and subject to type I error.[14]

We, therefore, sought to examine the influence of sarcopenia in a larger cohort of patients who received an SPK allograft.

MATERIALS AND METHODS

Patients

A total of 141 patients underwent SPK between October 2010 and July 2018 at the University of California, San Francisco. The patients were followed up until December 2019. There were no retransplants in this cohort. The patients without a perioperative computed tomography (CT) scan available (n = 34) were excluded from the analysis. Patient characteristics, demographic data, pancreas and kidney function, patient and overall graft survival (ie, nondeath censored graft survival), and deceased donor data were collected from chart review, administrative databases, and the United Network for Organ Sharing database. Pancreas Donor Risk Index was calculated as previously described.[15] Delayed graft function was defined as patients requiring hemodialysis in the first week after transplantation. Infection was defined as clinical symptoms of infection and the need for hospitalization within 6 months after transplantation (including urinary tract infections, surgical site infections, abscesses, pneumonia, and sepsis). Kidney and pancreas rejection was defined based on kidney and pancreas biopsy results. Kidney graft failure was defined as the return to dialysis or patient death. Pancreas graft failure was defined as the reintroduction of insulin therapy or patient death. The study was approved by the Committee for Human Research at University of California, San Francisco, and met criteria for waiver of consent.

Calculation of Psoas Muscle Index

PMI was measured on perioperative CT scan performed either within 2.8 years before transplant (n = 31) or up to 2.3 months after transplant (n = 76). Among the 31 patients with a preoperative CT, 22 (71%) had a CT >1 year before transplant. Among the 76 patients with a postoperative CT, 41 (54%) had a CT within 2-weeks posttransplant. CT images at the level of the fourth/fifth lumbar vertebrae and Image J software (National Institute of Health, Bethesda, MD) were used to measure the cross-sectional area of the right and left psoas muscles. Measurements were done by H.N. and R.P.H.M., blinded to group assignment and outcomes. The PMI was then calculated as per conventions that were previously described[6,14]: PMI as the cross-sectional area of bilateral psoas muscle^2/height^2 (cm^2/m^2). Because the range of PMI in men and women is different, a low PMI was defined as the lowest quartile for men and women separately. We divided the recipients into 2 groups using the lower quartile values as the threshold separating patients with a normal PMI from those with a low PMI (normal PMI in men and women was ≥7.43 and ≥6.20 cm^2/m^2, respectively; low PMI in men and women was <7.43 and <6.20 cm^2/m^2, respectively). In patients with a low PMI, we identified those with a follow-up CT scan of the abdomen and measured a follow-up PMI in these patients (n = 12).

Statistical Analyses

Results are presented as mean ± SD and as count and percentage for categorical variables unless specified otherwise. Differences between groups were analyzed with the *t* test for continuous variables and the Chi-square test for binary and categorical variables. Survival analyses were performed with the Kaplan-Meier method, and groups were compared using the log-rank test. Technical and early failures (within the first 40 d) were excluded from the pancreas survival analysis (n = 2). Univariate and multivariate Cox proportional-hazards regression was used to compute hazard ratios. Variables with a $P < 0.10$ in the univariate analysis were included in the multivariate analysis. Correlations and corresponding *P* values were assessed using linear regression. Ninety-five percent confidence intervals were reported, and an exact 2-sided $P < 0.05$ was considered statistically significant. Statistical data and graphs were generated using SPSS version 24.0 (SPSS, Chicago, IL) and Prism version 8 (GraphPad, San Diego, CA).

RESULTS

Baseline Characteristics and Short-term Outcomes

A total of 107 patients were assigned to either the low PMI group (the lowest quartile, n = 23) or the normal PMI group (above the lowest quartile, n = 84). On average, CT scan was performed 2.0 ± 5.9 and 2.3 ± 6.9 months before the surgery in the low and high PMI groups, respectively ($P = 0.820$). Patient and donor characteristics are shown in Table 1. Recipient BMI was significantly lower in the low PMI group compared with the normal PMI group (22.5 ± 3.8 versus 25.8 ± 3.3 kg/m^2, $P < 0.001$), and a weak correlation was identified between PMI and BMI ($R^2 = 0.107$, $P < 0.001$) (Figure 1A). All the other baseline characteristics were not statistically different between the 2 groups. Panel-reactive antibody (PRA), HLA mismatches, and preoperative donor–specific antibodies were not statistically different between groups; all recipients received thymoglobulin and steroids for induction, and baseline maintenance immunosuppression was similar between the 2 groups. Preoperative serum albumin was not correlated with PMI (Figure 1B). Diabetes duration and preoperative HbA1c were also not different between the low and normal PMI groups. Patient and transplant outcomes are presented

TABLE 1.

Characteristics of simultaneous pancreas-kidney transplant recipients according to their initial PMI

Characteristics	Low PMI (n = 23)	Normal PMI (n = 84)	P[a]
Recipient factors			
PMI (cm^2/m^2)	6.3 ± 0.9	8.7 ± 1.6	<0.001
Age at transplant, y	40.0 ± 7.0	40.7 ± 7.2	0.686
Gender (%)			
Male	15 (65.2)	48 (57.1)	0.486
Female	8 (34.8)	36 (42.9)	
Preoperative BMI, kg/m^2	22.5 ± 3.8	25.8 ± 3.3	<0.001
Duration since DM diagnosis, y	28.1 ± 10.5	27.7 ± 8.9	0.874
Duration of dialysis, y	2.5 ± 1.5	2.6 ± 2.3	0.860
Preoperative hemoglobin A1c, %	8.2 ± 1.4	8.1 ± 1.7	0.789
Preoperative serum albumin, g/dL	3.66 ± 0.46	3.60 ± 0.47	0.603
Race/ethnicity (%)			
White	9 (39.1)	44 (52.4)	0.259
African	3 (13.0)	20 (23.8)	
Hispanic	7 (30.4)	13 (15.5)	
Asian	2 (8.7)	4 (4.8)	
Hawaii	2 (8.7)	3 (3.6)	
PRA (%)	12.3 ± 24.6	15.1 ± 24.3	0.622
HLA mismatches			
2	1 (4.3)	7 (8.3)	0.549
3	1 (4.3)	8 (9.5)	
4	5 (21.7)	26 (31.0)	
5	9 (39.1)	28 (33.3)	
6	7 (30.4)	15 (17.9)	
Preoperative positive DSA			
Present	0 (0.0)	2 (2.4)	0.999
Absent	23 (100.0)	82 (97.6)	
Maintenance immunosuppression			
Tacrolimus	21 (91.3)	76 (90.5)	0.999
Mycophenolate	23 (100.0)	84 (100.0)	N/A
mTOR inhibitor	0 (0.0)	3 (3.6)	0.999
Azathioprine	0 (0.0)	1 (1.2)	0.999
Other	2 (8.7)	8 (9.5)	0.999
Steroid (%)			
Withdrawal	16 (69.6)	41 (48.8)	0.100
Maintenance	7 (30.4)	43 (51.2)	
Diabetes type			
Type 1	21 (91.3)	80 (95.2)	0.607
Type 2	2 (8.7)	4 (4.8)	
Donor factors			
Age, y	24.7 ± 7.7	23.7 ± 7.2	0.578
Gender (%)			
Male	17 (73.9)	62 (73.8)	0.999
Female	6 (26.1)	22 (26.2)	
BMI, kg/m^2	23.0 ± 3.0	23.9 ± 3.5	0.286
Cause of death			
Anoxia	8 (34.8)	21 (25.0)	0.643
Cerebrovascular	2 (8.7)	9 (10.7)	
Head trauma	13 (56.5)	54 (64.3)	
Donor terminal creatinine, mg/dL	0.81 ± 0.28	0.82 ± 0.25	0.822
KDPI (%)	13.3 ± 8.6	10.7 ± 10.8	0.295
PDRI	0.96 ± 0.15	0.97 ± 0.25	0.857
Cold ischemic time, h	11.2 ± 5.3	10.4 ± 3.7	0.432

[a]Student *t* test for continuous variables; X^2 test for binary or categorical variables (global *P* value). Data are presented as mean ± SD or n (%).

BMI, body mass index; DM, diabetes mellitus; DSA, donor-specific antibody; KDPI, Kidney Donor Profile Index; mTOR, mammalian target of rapamycin; PDRI, Pancreas Donor Risk Index; PMI, psoas muscle mass index; PRA, panel-reactive antibody.

in Table 2. The median follow-up was 4 years in both groups ($P = 0.365$). Short-term outcomes including surgical complications (assessed using the Clavien-Dindo score[16]), delayed graft function, rejection, infection, and length of hospital stay were not statistically different between groups.

Pancreas Graft Survival

Overall, pancreas graft survival was 83.4% at 5 years. We observed that patient in the low PMI group had reduced pancreas graft survival compared with patients in the normal PMI group ($P = 0.031$) (Figure 2A). The survival rates were 79.9% and 86.7% at 5 years in the low and normal PMI group, respectively. Accordingly, hemoglobin A1c at last follow-up was higher in patients with low PMI; however, the difference between groups was not present anymore after the exclusion of patients with failed pancreas allografts (Table 2). A sensitivity analysis comparing patients with and without a CT scan before or after surgery showed no difference in terms of pancreas graft survival (Figure S1A and S1B, SDC, http://links.lww.com/TXD/A279). Among the 6 pancreas graft losses in the low PMI group, 3 were due to rejection, and 2 were due to diabetes recurrence, whereas among the 9 graft losses in the normal PMI group, 3 were due to vascular complications, and 1 was due to rejection (Table 3). The predictors of pancreas survival outcomes were analyzed in a Cox regression model (Table 4). In the univariate analysis, female gender, black or African American race, higher PRA, and low PMI were associated with pancreas allograft failure. Of note, lower recipient BMI was not associated with a decreased pancreas graft survival (Table 4 and Figure S1C, SDC, http://links.lww.com/TXD/A279). All variables with a $P < 0.1$ in the univariate analysis were then included in the multivariate Cox regression. Patients with a low PMI were 5 times more likely to lose their pancreas allograft (hazard ratios, 5.4; 95% confidence intervals, 1.4-20.8; $P = 0.015$), and PMI was the only independent significant predictor in the multivariate analysis among the significant variables in the univariate analysis (ie, gender, race, PRA, steroid use, PMI, and Kidney Donor Profile Index) (Table 4).

Evolution of Sarcopenia After Transplant

We identified 12 patients in the low PMI group for which a follow-up CT scan of the abdomen was available. Follow-up CT scans were obtained 3.0 ± 2.8 years after transplant. Of the patients who progressed toward pancreas failure, 75.0% (3/4) had a decrease in PMI, as compared with 37.5% (3/8) in the patients who had a functioning pancreas allograft at the end of the follow-up (Figure 3). Two patients who had initial low PMI and who did not lose their graft had improvement in their sarcopenia after transplant and had a normal PMI at the end of the follow-up (Figure 3, patients 5 and 7). Interestingly, BMI differences between normal and low PMI groups observed before transplant were partially corrected after transplant (Table 2). No difference in kidney or pancreas graft survival was observed among patients with versus without a follow-up CT scan (Figure S2A and S2B, SDC, http://links.lww.com/TXD/A279).

Kidney Graft Survival and Overall Survival

Overall kidney graft survival was 91.7% at 5 years. Creatinine levels were not different between groups at the end of follow-up (Table 2). The kidney survival rate was not affected by initial PMI status (Figure 2B). Overall patient survival was 95.4% at 5 years. No statistically significant difference in patient survival was observed between the low and normal PMI groups (Figure 2C).

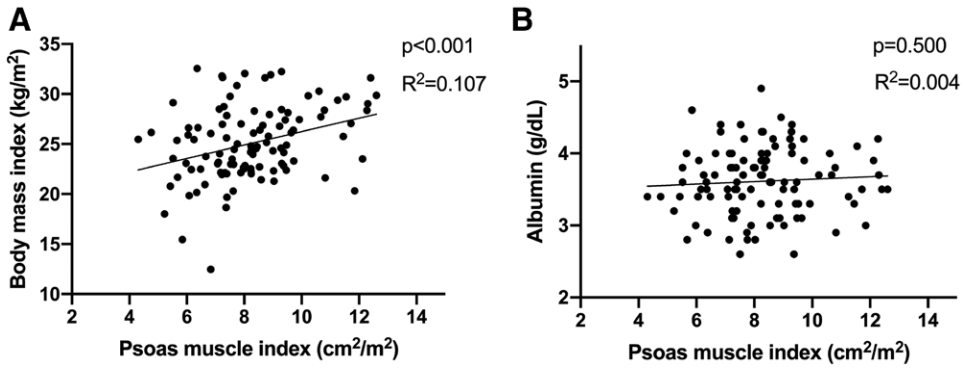

FIGURE 1. Psoas muscle index relation with body mass index and serum albumin. (A) Psoas muscle index (cm^2/m^2) stratified by preoperative body mass index (kg/m^2). A weak relationship is noted between body mass index and body mass index. (B) Psoas muscle index stratified by preoperative serum albumin (g/dL). No relationship was identified. R^2 and *P* values were calculated using linear regression.

DISCUSSION

In the current study, we measured muscle mass in SPK transplant recipients to analyze potential associations between sarcopenia and posttransplant outcomes. We found that a low PMI in SPK recipients was associated with significantly lower long-term pancreas graft survival rates. Rejection and diabetes recurrence were the main causes of pancreas graft loss in recipients with a low psoas muscle index. Kidney graft survival and overall patient survival were not affected by initial PMI status.

TABLE 2.

Patient and transplant outcomes according to their initial recipient PMI

Parameter	Low PMI (n = 23)	Normal PMI (n = 84)	*P*[a]
Short-term outcomes			
Surgical complication (Clavien-Dindo classification)			
None	9 (39.1)	21 (25.0)	0.652
1	1 (4.3)	6 (7.1)	
2	6 (26.1)	28 (33.3)	
3a	2 (8.7)	16 (19.0)	
3b	3 (13.0)	10 (11.9)	
4a	1 (4.3)	2 (2.4)	
4b	1 (4.3)	1 (1.2)	
Delayed graft function (%)			
Present	2 (8.7)	7 (8.3)	0.870
Absent	21 (91.3)	76 (90.5)	
Unknown	0 (0.0)	1 (1.2)	
Biopsy proven rejection (kidney)			
Present	4 (17.4)	19 (22.6)	0.638
Absent	15 (65.2)	56 (66.7)	
No biopsy done/available	4 (17.4)	9 (10.7)	
Biopsy proven rejection (pancreas)			
Present	1 (4.3)	8 (9.5)	0.539
Absent	0 (0.0)	2 (2.4)	
No biopsy done/available	22 (95.7)	74 (88.1)	
Infection, any (%)			
Present	5 (21.7)	23 (27.4)	0.790
Absent	18 (78.3)	61 (72.6)	
Length of postoperative hospital stay (d)	10.3 ± 6.0	10.2 ± 5.3	0.989
Long-term outcomes			
Median follow-up, y (min–max)	4.0 (1.1–9.1)	4.0 (0.5–9.0)	0.365[b]
Number of hospital readmission	2.9 ± 3.3	3.1 ± 3.1	0.763
Hemoglobin A1c at last follow-up (all patients)	6.0 ± 1.7	5.5 ± 1.0	0.037
Hemoglobin A1c (excluding patients with a nonfunctioning pancreas allograft)	5.2 ± 0.3	5.2 ± 0.5	0.817
Serum creatinine level at last follow-up	1.2 ± 1.2	1.2 ± 0.5	0.890
BMI at last follow-up, kg/m^2	25.6 ± 4.1	27.5 ± 5.4	0.137
BMI change from transplant to last follow-up	+2.8 ± 3.4	+1.7 ± 4.2	0.228

[a]Student t-test for continuous variables, X^2 test for binary or categorical variable (global *P* value).
[b]Mann-Whitney *U* test.
Data are presented as mean ± SD or n (%) unless indicated otherwise.
BMI, body mass index; PMI, psoas muscle mass index.

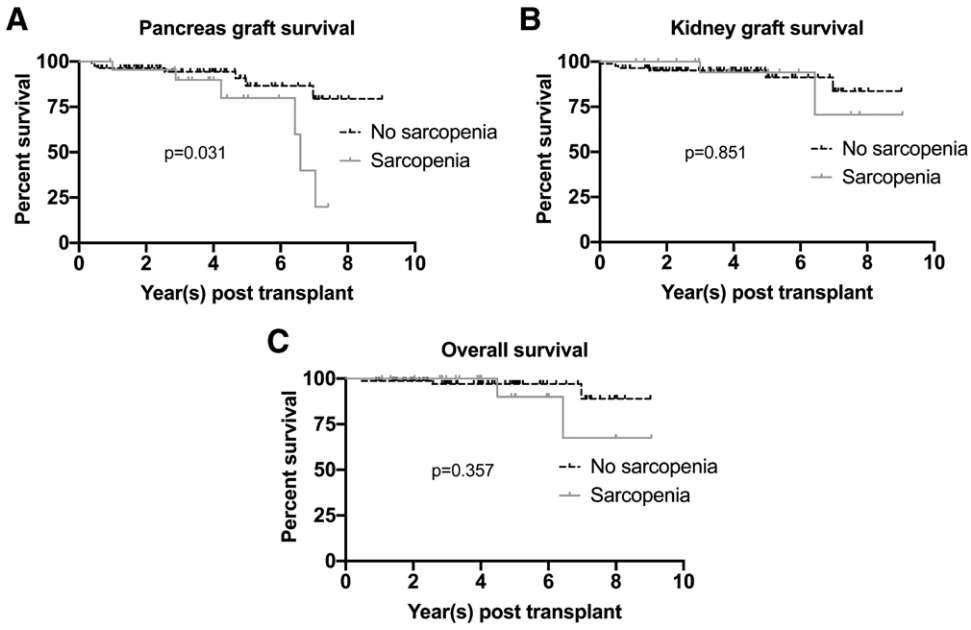

FIGURE 2. Kaplan-Meier survival curves for simultaneous pancreas-kidney transplant and patient survival. (A) Pancreas graft, (B) kidney graft, and (C) overall patient survival stratified by initial psoas mass index status, that is, low PMI (Sarcopenia) vs normal PMI (no sarcopenia). *P* values were calculated using the log-rank test. Technical and early failures (within the first 40 days) were excluded from the pancreas survival analysis (n = 2).

Sarcopenia is defined as a loss of skeletal muscle mass and function[17] and is associated with frailty, mortality, and poor outcomes in both surgical and nonsurgical patients.[18] Frailty is defined by the presence of 3 of the following items: low-grip strength, low energy, slowed waking speed, low-physical activity, and unintentional weight loss.[19] Risk factors for sarcopenia include age, gender, level of physical activity, malnutrition, and various comorbid conditions.[17,18,20] Interestingly, type 1 diabetes was associated with sarcopenia via the accumulation of advanced glycation end products.[21] Sarcopenia has previously been shown to be associated with higher mortality rates after liver transplantation,[5,22] living donor liver transplantation,[7] and abdominal aortic aneurysm repair,[23] as well as higher postoperative infection risk and delayed recovery from colorectal cancer resection surgery[24] and laparotomy.[25]

TABLE 3.

Pancreas status at the end of follow-up among low and high PMI groups

	Low PMI (n = 23)	Normal PMI (n = 84)	*P*[a]
Functioning pancreas	17 (73.9)	75 (89.3)	0.026
Rejection[b]	3 (13.0)	1 (1.2)	
Diabetes recurrence[b]	2 (8.7)	0 (0.0)	
Cancer[b]	1 (4.3)	1 (1.2)	
Vascular complication[c]	0 (0.0)	3 (3.6)	
Infection[b]	0 (0.0)	1 (1.2)	
Nonadherence[b]	0 (0.0)	1 (1.2)	
Pancreatic leak[b]	0 (0.0)	1 (1.2)	
Unknown cause[b]	0 (0.0)	1 (1.2)	

[a]X^2 test (global *P* value).
[b]Causing pancreas graft loss.
[c]Including 1 artery thrombosis, 1 vein thrombosis, and 1 artery aneurysm.
Data are presented as n (%).
BMI, body mass index; PMI, psoas muscle mass index.

Our results are consistent with those of a previous study that linked skeletal muscle quality, quantified by the intramuscular (psoas) adipose tissue content, to a higher risk of postoperative complications and unfavorable pancreas graft survival.[6] The authors reported that recipients with a lower PMI had a lower pancreas survival; however, the difference was not statistically significant, possibly due to the low number of participants in this study. With a larger cohort, we demonstrate a significant association between low PMI and unfavorable pancreas graft survival. This observation was further confirmed in our multivariate model. The differences were seen in the mid- to long-term survival and suggest that sarcopenia persists after transplantation. Data on those who had a follow-up CT scan after transplant further reinforce this hypothesis: 62.5% (5/8) of the patients with low initial PMI and a functioning graft at the end of the follow-up either improved their PMI (37.5%) or resolved sarcopenia (25.0%). On the other hand, 75.0% (3/4) of the patients with a low PMI who lost their pancreas allograft also continued to lose muscle mass. In the Cox univariate analysis, sarcopenia, female gender, Black or African American race,[4] and higher PRA were associated with a lower pancreas graft survival. The multivariate Cox model highlighted the significant role of PMI, which remained the sole predictor of pancreas graft survival in our model. Some other well-known risk factors for graft failure after SPK include young age, a BMI over 30 kg/m^2, older donor age, and longer preservation time.[4] We could not significantly highlight all of them in our cohort, possibly due to a lack of power. Interestingly, we found a weak correlation between recipient PMI and BMI. One could ask whether recipient BMI could be a predictor of pancreas graft survival as well. In the Scientific Registry of Transplant Recipients dataset, similarly to overweight, underweight (BMI < 18.5 kg/m^2) was associated with unfavorable outcomes after SPK.[26] This report in line with our correlation between BMI and PMI, and the detrimental roles of

TABLE 4.

Estimated hazard ratios for pancreas survival using a multivariate Cox proportional hazard model

	Univariate analysis			Multivariate analysis		
Parameter	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Recipient factors						
Tx age, y	0.9	0.9-1.0	0.173			
Gender, female	4.5	1.2-16.3	0.023	2.6	0.7-10.5	0.174
Preoperative BMI, kg/m^2	0.9	0.8-1.1	0.443			
Duration since diagnosis DM, y	1.0	0.9-1.0	0.488			
Duration of dialysis, mo	1.1	0.8-1.5	0.537			
Preoperative HbA1c, %	1.1	0.8-1.5	0.454			
Preoperative serum albumin, g/dL	1.3	0.4-4.2	0.617			
Race/ethnicity (%)						
White	1 [Ref.]	NA	NA	1 [Ref.]	NA	NA
Black or African American	4.4	1.2-15.7	0.024	1.4	0.3-6.1	0.636
Hispanic	2.3	0.5-10.3	0.278	0.7	0.1-4.2	0.713
Asian	0.0	0.0-NR	0.993	0.0	0.0-NR	0.990
Hawaii	0.0	0.0-NR	0.992	0.0	0.0-NR	0.990
Panel-reactive antibody	1.0	1.0-1.0	0.015	1.0	1.0-1.0	0.203
DM type (1:2)	1.8	0.3-19.5	0.405			
Steroid use, withdrawal	3.4	0.9-12.6	0.061	3.6	0.7-19.2	0.135
Low PMI	3.1	1.1-9.3	0.041	5.4	1.4-20.8	0.015
Donor factors						
Age, y	1.1	1.0-1.1	0.152			
Gender, male	1.0	0.3-3.8	0.973			
BMI, kg/m^2	1.0	0.8-1.2	0.955			
Cause of death						
Head trauma	1 [Ref.]	NA	NA			
Cerebrovascular	1.8	0.4-8.5	0.486			
Anoxia	1.7	0.5-5.7	0.423			
Donor terminal creatinine	2.5	0.3-23.7	0.405			
KDPI, %	77.7	0.5-NR	0.089	392.8	0.6-NR	0.073
Cold ischemic time, h	0.9	0.8-1.1	0.433			

Technical and early failures (within the first 40 d) were excluded from the analysis (n = 2).
BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; PMI, psoas muscle mass index; NR, not reported (values superior to 6000).

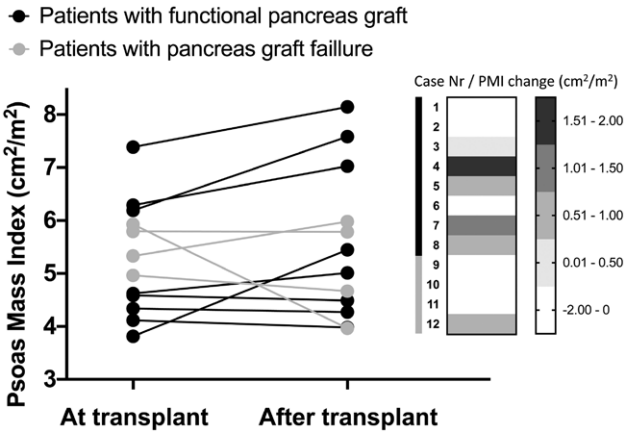

FIGURE 3. A Psoas muscle index at and after transplant in patient with an initial low psoas muscle index and an available follow-up CT scan. Patients who progressed towards pancreas failure (gray dots and lines) and who had a functioning pancreas allograft at the end of the follow-up (black dots and lines) are represented. A heatmap representing the intensity patient's PMI change is represented on the right. Patients 1–8 had a functioning pancreas allograft at the end of the follow-up, and patients 9–12 had a pancreas graft failure. CT, computed tomography; PMI, psoas muscle index.

sarcopenia and frailty as shown by us and others.[27] We could not highlight a significant association between low BMI and pancreas graft survival (possibly because only 3 recipients had a BMI < 18.5 kg/m^2 in our cohort).

Given our findings, we believe that sarcopenia might represent an important predictive factor that should be measured in SPK candidates. Currently, every SPK patient listed at our center gets a noncontrast CT scan to measure PMI; we are in the process of implementing the measurement of grip strength, timed chair stands, and balance testing to estimate frailty. This could have an important impact because the preoperative identification of sarcopenia would allow for intervention on these potentially modifiable risk factors. Of note, progressive resistance training and nutrition modifications represent excellent interventions to reverse sarcopenia.[28] Successful interventions on sarcopenia would be conditional to the control of other well-established risk factors such as recipient age, BMI, donor age, and preservation time.[4]

The mechanism by which sarcopenia is associated with lower pancreas survival remains to be elucidated. Given the low number of events, it is hard to speculate regarding the potential link between sarcopenia and pancreas graft loss. Pancreas graft loss is often multifactorial, and the result of multiple accumulating adverse events. It is possible that

sarcopenic patients suffer more indirect risks (including more severe postoperative complications, subclinical infections, rejections, etc), which collectively diminish pancreas graft lifespan. This progressive accumulation of "hits" is consistent with the slow and gradual survival difference observed between low and normal PMI groups. These gradual differences could be further explained by the fact that patients can maintain normoglycemia until very late in the process of graft loss, tolerating losses of up to 80% of their beta-cell mass.[29] In our cohort, overall complication rates were not statistically different between groups. However, severe complications (ie, Clavien-Dindo ≥3b) were more frequent in the low PMI group (21.6% versus 15.5%). On the other hand, less severe complications were more frequent in the normal PMI group (59.4% versus 39.1%).

We observed that 3 out of 6 pancreas failures were due to rejection in the low PMI group. This is consistent with what we previously observed in liver transplant recipients, in whom frailty was associated with increased rates of acute cellular rejection.[30] Potential mechanisms for these higher rejection rates imply that frail patients have an increased inflammatory state[31] and tend to experience *higher* rates of mycophenolate dose reduction than nonfrail recipients.[30] In other words, one could hypothesize that low PMI patients receive less immunosuppression because the management team is more prone to reduce doses to avoid overimmunosuppression-related complications in these frail patients.

Another potential important mechanistic explanation is that the muscle mass itself and exercise have a direct protective effect on β-cells survival and function.[32] Of note, sarcopenia was demonstrated to exacerbate obesity-associated insulin resistance and dysglycemia.[33,34] The secretion of interleukins-6 by the muscle was shown as one of the important mediators of this effect.[32,35,36] Another important factor is fibroblast growth factor 21, a known β-cell protective factor, which is secreted by the muscle in response to insulin.[37] In response to saturated fatty acids, muscles also produce irisin, which, when administrated in vivo, promotes β-cell survival and enhanced glucose-stimulated insulin secretion.[38] Considering this cross talk between myocytes and β cells, it is also interesting to note that in contrast with pancreas-related outcomes, sarcopenia was not significantly associated with kidney graft survival in our cohort. This may be related to the fact that the kidney grafts typically have better survival rates compared with pancreas grafts. The link between catabolism and glucose homeostasis possibly makes the pancreas more sensitive compared with the kidney. We did not observe a significant difference in terms of overall patient survival between low PMI and normal PMI patients. The overall low-mortality rate in our cohort possibly prevented us from observing a significant difference.

The present study does have some limitations. First, we report on a small cohort of patients from a single transplant center, and the retrospective nature of our study does not allow definitive conclusions on causality. With this limited number of cases, results, especially regarding causes of pancreatic graft loss, need to be interpreted with caution. Further studies including multicenter data are warranted to confirm the impact of sarcopenia in this realm. Second, there is a limited selection bias in the study group because we only included patients with a CT scan of the abdomen in the perioperative period (n = 107), although excluded patients represented a limited percentage (19.9%, 28/141). With sensitivity analysis, we found that pancreas graft survival was not different between patients with and without a CT scan. In addition, we only compared graft survival rates among patients who had a CT scan of the abdomen, and our conclusions should, therefore, remain valid. We also acknowledge the fact that not all CT scans were done immediately before surgery, which would represent the ideal time for the measure. However, most of the CT scans were performed before or shortly after surgery, and there was no difference in CT scan dates between groups or difference in pancreas graft survival with different CT scan dates. Moreover, sarcopenia takes time to reverse,[39] and, in the absence of pre/perioperative resistance training or nutritional intervention, it is unlikely to improve before or immediately after transplant. We, therefore, believe that the observed values represent acceptable estimates of muscle mass at transplant in our population. It is also important to note that in this study, we describe only 1 component of frailty, namely, sarcopenia, in a young population of patients. We recognize that the notion of sarcopenia has been developed and best assessed in geriatric populations. Future prospective studies will be able to gather more refined measurements of sarcopenia and potentially include an intervention to tackle the detrimental effect of muscle mass loss before transplant.

In conclusion, sarcopenia was associated with decreased pancreas graft survival in patients receiving an SPK transplant. The known protective role of an adequate muscle mass on β-cell function may explain these findings. The systematic identification of sarcopenia in SPK candidates can help to identify patients with diminished physiological buffer. Intervention with resistance training and nutrition modifications could be implemented for patients with muscle mass loss to reverse sarcopenia and potentially improve posttransplant outcomes.

ACKNOWLEDGMENTS

We thank Anna Mello for her help with the patient database management.

REFERENCES

1. Gruessner RW, Gruessner AC. The current state of pancreas transplantation. *Nat Rev Endocrinol.* 2013;9:555–562.
2. Smets YF, Westendorp RG, van der Pijl JW, et al. Effect of simultaneous pancreas-kidney transplantation on mortality of patients with type-1 diabetes mellitus and end-stage renal failure. *Lancet.* 1999;353:1915–1919.
3. Becker BN, Brazy PC, Becker YT, et al. Simultaneous pancreas-kidney transplantation reduces excess mortality in type 1 diabetic patients with end-stage renal disease. *Kidney Int.* 2000;57:2129–2135.
4. Gruessner AC, Gruessner RWG. Pancreas transplantation for patients with type 1 and type 2 diabetes mellitus in the United States: a registry report. *Gastroenterol Clin North Am.* 2018;47:417–441.
5. Englesbe MJ, Patel SP, He K, et al. Sarcopenia and mortality after liver transplantation. *J Am Coll Surg.* 2010;211:271–278.
6. Fukuda Y, Asaoka T, Eguchi H, et al. Clinical impact of preoperative sarcopenia on the postoperative outcomes after pancreas transplantation. *World J Surg.* 2018;42:3364–3371.
7. Hamaguchi Y, Kaido T, Okumura S, et al. Impact of quality as well as quantity of skeletal muscle on outcomes after liver transplantation. *Liver Transpl.* 2014;20:1413–1419.
8. Kaido T, Uemoto S. Direct segmental multi-frequency bioelectrical impedance analysis is useful to evaluate sarcopenia. *Am J Transplant.* 2013;13:2506–2507.
9. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al; European Working Group on Sarcopenia in Older People. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in older people. *Age Ageing.* 2010;39:412–423.

10. Peng PD, van Vledder MG, Tsai S, et al. Sarcopenia negatively impacts short-term outcomes in patients undergoing hepatic resection for colorectal liver metastasis. *HPB (Oxford).* 2011;13:439–446.
11. Peng P, Hyder O, Firoozmand A, et al. Impact of sarcopenia on outcomes following resection of pancreatic adenocarcinoma. *J Gastrointest Surg.* 2012;16:1478–1486.
12. Hamaguchi Y, Kaido T, Okumura S, et al. Preoperative intramuscular adipose tissue content is a novel prognostic predictor after hepatectomy for hepatocellular carcinoma. *J Hepatobiliary Pancreat Sci.* 2015;22:475–485.
13. Okumura S, Kaido T, Uemoto S. Reply to: Impact of the preoperative quantity and quality of skeletal muscle on outcomes after resection of extrahepatic biliary malignancies. *Surgery.* 2016;159:1695–1696.
14. Noguchi H, Miyasaka Y, Kaku K, et al. Preoperative muscle volume predicts graft survival after pancreas transplantation: a retrospective observational cohort study. *Transplant Proc.* 2018;50:1482–1488.
15. Axelrod DA, Sung RS, Meyer KH, et al. Systematic evaluation of pancreas allograft quality, outcomes and geographic variation in utilization. *Am J Transplant.* 2010;10:837–845.
16. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg.* 2004;240:205–213.
17. Santilli V, Bernetti A, Mangone M, et al. Clinical definition of sarcopenia. *Clin Cases Miner Bone Metab.* 2014;11:177–180.
18. Friedman J, Lussiez A, Sullivan J, et al. Implications of sarcopenia in major surgery. *Nutr Clin Pract.* 2015;30:175–179.
19. Xue QL. The frailty syndrome: definition and natural history. *Clin Geriatr Med.* 2011;27:1–15.
20. Muscaritoli M, Anker SD, Argilés J, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: Joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". *Clin Nutr.* 2010;29:154–159.
21. Mori H, Kuroda A, Araki M, et al. Advanced glycation end-products are a risk for muscle weakness in Japanese patients with type 1 diabetes. *J Diabetes Investig.* 2017;8:377–382.
22. van Vugt JL, Levolger S, Metselaar HJ, et al. Reply to: Comparing the variability between measurements for sarcopenia using magnetic resonance imaging and computed tomography imaging. *Am J Transplant.* 2016;16:2768.
23. Lee JS, He K, Harbaugh CM, et al; Michigan Analytic Morphomics Group (MAMG). Frailty, core muscle size, and mortality in patients undergoing open abdominal aortic aneurysm repair. *J Vasc Surg.* 2011;53:912–917.
24. Lieffers JR, Bathe OF, Fassbender K, et al. Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. *Br J Cancer.* 2012;107:931–936.
25. Lee JS, Terjimanian MN, Tishberg LM, et al. Surgical site infection and analytic morphometric assessment of body composition in patients undergoing midline laparotomy. *J Am Coll Surg.* 2011;213:236–244.
26. Bédat B, Niclauss N, Jannot AS, et al. Impact of recipient body mass index on short-term and long-term survival of pancreatic grafts. *Transplantation.* 2015;99:94–99.
27. Parsons R, Wolosyn J, Lynch R. Morphometric and metabolic correlates of frailty in pancreas transplant recipients. *Am J Transplant.* 2018;18:432.
28. Cruz-Jentoft AJ, Landi F, Schneider SM, et al. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). *Age Ageing.* 2014;43:748–759.
29. Ris F, Niclauss N, Morel P, et al. Islet autotransplantation after extended pancreatectomy for focal benign disease of the pancreas. *Transplantation.* 2011;91:895–901.
30. Fozouni L, Mohamad Y, Lebsack A, et al. Frailty is associated with increased rates of acute cellular rejection within 3 months after liver transplantation. *Liver Transpl.* 2020;26:390–396.
31. Marcos-Pérez D, Sánchez-Flores M, Maseda A, et al. Frailty in older adults is associated with plasma concentrations of inflammatory mediators but not with lymphocyte subpopulations. *Front Immunol.* 2018;9:1056.
32. Christensen CS, Christensen DP, Lundh M, et al. Skeletal muscle to pancreatic β-cell cross-talk: the effect of humoral mediators liberated by muscle contraction and acute exercise on β-cell apoptosis. *J Clin Endocrinol Metab.* 2015;100:E1289–E1298.
33. Srikanthan P, Hevener AL, Karlamangla AS. Sarcopenia exacerbates obesity-associated insulin resistance and dysglycemia: findings from the National Health and Nutrition Examination Survey III. *PLoS One.* 2010;5:e10805.
34. Atlantis E, Martin SA, Haren MT, et al; Members of the Florey Adelaide Male Ageing Study. Inverse associations between muscle mass, strength, and the metabolic syndrome. *Metabolism.* 2009;58:1013–1022.
35. Ellingsgaard H, Hauselmann I, Schuler B, et al. Interleukin-6 enhances insulin secretion by increasing glucagon-like peptide-1 secretion from L cells and alpha cells. *Nat Med.* 2011;17:1481–1489.
36. Barlow J, Carter S, Solomon TPJ. Probing the effect of physiological concentrations of IL-6 on insulin secretion by INS-1 832/3 insulinoma cells under diabetic-like conditions. *Int J Mol Sci.* 2018;19:1924.
37. Hojman P, Pedersen M, Nielsen AR, et al. Fibroblast growth factor-21 is induced in human skeletal muscles by hyperinsulinemia. *Diabetes.* 2009;58:2797–2801.
38. Natalicchio A, Marrano N, Biondi G, et al. The myokine irisin is released in response to saturated fatty acids and promotes pancreatic β-cell survival and insulin secretion. *Diabetes.* 2017;66:2849–2856.
39. Tsien C, Shah SN, McCullough AJ, et al. Reversal of sarcopenia predicts survival after a transjugular intrahepatic portosystemic stent. *Eur J Gastroenterol Hepatol.* 2013;25:85–93.