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ORIGINAL ARTICLE

Isolated pancreas rejections do not have an adverse impact on kidney graft survival whereas kidney rejections are associated with adverse pancreas graft survival in simultaneous pancreas kidney transplantation

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Abstract

Background and objectives Diabetic Kidney Disease is associated with excessive mortality and morbidity. Simultaneous pancreas kidney transplantation (SPK) significantly improves quality of life and increases life expectancy of uremic diabetic patients. It is not known whether pancreas and kidney rejections in these transplant patients is concordant or discordant.

Design, setting, participants, and measurements We analyzed clinical data on all SPK transplants performed between 2003 and 2014 at Indiana University to assess the impact of isolated or combined pancreas and kidney rejections on patient and allograft outcomes. The primary outcome of interest was kidney graft rejection within 1 year of pancreatic rejection and kidney survival in SPK patients with and without pancreatic rejection.

Results Mean age of patients was 44 ± 9 years; 61.9% were males; 88% were Caucasians. A total of 23.8% of cases had rejection [8.7% pancreatic rejection alone (PA), 4.4% had concordant pancreas and kidney (PK) rejection, and 10.7% had kidney rejection alone(KA)]. PK had a worse effect on kidney graft survival than PA ($p = 0.019$). Neither pancreas rejection nor kidney rejection had an adverse effect on patient survival. However, both pancreas graft failure and kidney graft failure adversely affected patient survival. Tacrolimus levels were not significantly different in all groups over a 10 year period ($p = 0.4584$).

Conclusions Concordant pancreas kidney rejection is synergistically deleterious to kidney graft survival. Graft failure, not graft rejection, is adversely associated with patient survival.

Keywords Simultaneous · Pancreas · Kidney · Transplantation · Concordance

Introduction

Diabetic Kidney Disease (DKD) is associated with retinopathy, neuropathy, peripheral vascular disease, and increased cardiovascular morbidity and mortality [1]. Simultaneous pancreas kidney (SPK) transplantation has demonstrated superior kidney allograft survival in type 1 diabetics compared to Deceased Donor Kidney Transplants alone [2–5]. SPK also improves quality of life and increases life expectancy of patients with DKD [6, 7]. One and five year pancreas graft survival rates are now comparable to other solid organ transplants [8].

In SPK, the pancreas and kidney grafts are procured from the same donor; hence, it seems immunologically plausible that pancreas and kidney rejections should be concordant. Indeed, because the kidney is easier to biopsy and monitor, the status of the kidney graft is used to gauge the status of the pancreas graft in SPK. However, some studies suggest that pancreas and kidney rejections can be discordant [9–13].

Shapiro et al. performed kidney biopsies in seven patients who had elevated lipase and normal creatinine; they found Banff 1A acute cellular rejection in all of the seven kidney biopsies [9]. Gruessner et al. performed biopsies of kidney

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and pancreas grafts in pigs; they found isolated pancreas rejection episodes in only 3 of 26 biopsies (12%) [10]. Human biopsies have reported discordance in pancreas kidney rejection in 21–33% of biopsies; in 61–71% of these biopsies, the discordant rejections were in the pancreas grafts [11]. Biopsying the kidney in the setting of pancreas rejection is likely to show subclinical rejection or incidental findings, the significance of which is unclear. Therefore, it seems reasonable to distinguish between subclinical and clinical concordance.

Several UNOS studies have been done to probe this question of concordant pancreas and kidney rejections. In these studies, isolated rejections are defined as rejections that occur without clinically overt rejection of the other graft. Isolated rejections are expected to be associated with adverse outcomes such as loss of the second graft if subclinical concordance is clinically significant. Rejections that occur in the first year post-transplantation are thought to be most associated with unfavorable long term graft outcomes; hence, UNOS studies have mainly looked at rejection in the first year after SPK transplantation.

Reddy et al. showed that isolated kidney rejection decreased kidney allograft survival but isolated pancreas rejections had no impact on kidney allograft survival [12]. However, their study was limited to the years 1988–1997. Claiming that this study was only over 5 years and that the immunosuppression available in that time period was inferior, Kaplan et al. performed a UNOS study from 1995 to 2006 [13]. Kaplan et al. showed that pancreas alone rejections were associated with an adverse effect on kidney graft survival. However, their study also showed that kidney alone rejections were not associated with adverse kidney graft survival. It must be noted that Banff criteria for classifying kidney rejections were not reported til 1997 and were not routinely in use til several years later. Induction with thymoglobulin was also not routine until 2000.

Although concordance is probable given the immunologic etiology of rejection and the immunogenicity of the pancreas, the immunologic process may be prolonged and concordant rejection is unlikely to be only just simultaneous. The half-life of memory T cells has been reported to be anywhere between 500 days [14] and 2 years [15]. Moreover, it is thought that these memory cells remain active due to continuous low-level stimulation of class II-restricted CD^{4+} T cells. Finally, over a longer period of time, memory cells may return to a resting state indistinguishable from naïve T cells [15]. Hence, it seems reasonable to define clinical concordance by rejections that are clinically overt and that occur within a year of each other. With these criteria, pancreas or kidney rejections without evidence of clinical rejection of the other graft within 1 year would be considered isolated rejections. Moreover, if isolated graft rejection is truly isolated, it would be less likely to be associated with adverse outcomes such as loss of the second graft. Indeed, Reddy et al. showed that isolated kidney rejection decreased kidney allograft survival but isolated pancreas rejections had no impact on kidney allograft survival [12].

We hypothesized that clinically overt concordant pancreas kidney rejections (PK) are more likely to be associated with kidney allograft loss. We also evaluated whether PK, PA, and KA patients were associated with adverse pancreas, kidney or patient survival. All cases were characterized by progression of creatinine, glucose, and Hba1c over 10 years.

Materials and methods

The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the 'Declaration of Istanbul on Organ Trafficking and Transplant Tourism'.

This is a single center study on all SPK transplants performed at Indiana University from 2003 to 2014. The study included all patients who were above 18 years of age. Patients whose grafts survived less than a year were excluded since these were not characterized by clinically concordant rejections and our definition of concordance required a year of followup. Multiple organ transplants other than SPK were also excluded as were surgical failures or clotted grafts. Treatment of pancreas and kidney rejections was with solumedrol; anti-thymocyte globulin was used if solumedrol failed.

The primary variable of interest was type of acute rejection (pancreas alone, kidney alone, or both pancreas and kidney within 1 year of each other). Acute rejection of the kidney was defined as an increase in creatinine by 0.3 mg/dL or by more than 20% from baseline along with biopsy evidence of acute cellular rejections. Acute rejection of the pancreas was diagnosed if one of the following was present: (1) a twofold rise in lipase from baseline (although any meaningful increase in serum lipase was thoroughly investigated), (2) Hyperglycemia (defined as fasting serum glucose greater than 126 mg/dL) (3) Response to glucocorticoids and (4) painful graft. The primary outcome of interest was kidney and pancreas graft status beyond the first post-transplant year. Recipient characteristics that were evaluated were race, gender, age, maintenance immunosuppression, and presence or absence of hypertension and hyperlipidemia.

General demographic and clinical variables, including HLA (Human Leukocyte Antigens) and PRA (Panel Reactive Antibodies) outcomes, were analyzed with Fisher's Exact Tests, due to low cell counts, to determine if there was a significant deviation from homogeneity between the four groups. The progression over time of Creatinine, Tacrolimus levels (FK), Glucose, and HbA1c were analyzed using repeated measures models, to account for the within

participant correlation. Generalized estimating equation (GEE) models were used to properly model this correlation, as well as ensuring the appropriate distribution was used to model the data.

Survival analyses were performed to determine if there were differences between four acute rejection categories using the log-rank test, in survival time. Acute rejections were assessed according to four categories: no rejection, pancreas alone, kidney alone or concordant pancreas/kidney. Patient survival, using time until death, was modeled not only for the four groups, but also looking at pancreas failure and kidney failure, in separate models with two groups (failure vs non-failure). Survival curves and log-rank tests were also generated for the time until pancreas failure and time until kidney failure. It is important to note that there is a time-bearing covariate. That is, rejection episodes could have occurred at different times, and that the longer a patient has their functioning graft, then they can still have a rejection episode. But if they do not have a functioning graft, they cannot or are unlikely to have a rejection episode. Hence, we used failure as a censoring variable in the analyses, which takes into consideration the time-bearing covariate mentioned above. Cox proportional hazards models were also performed in order to account for rejection time (the time from transplant date until date of acute rejection).

All analytic assumptions were verified for each model and all analyses were performed using SAS v9.4 (SAS Institute, Cary, NC).

Results

Characteristics

We analyzed 252 SPK transplants that were performed between 2003 and 2014. Mean age of patients was 44 ± 9 years; 61.9% were males; 88% were caucasians. Table 1 depicts characteristics by acute rejection category. Anti-thymocyte Antibody (Thymoglobulin) is used for induction therapy at Indiana University with a steroid free maintenance regimen of immunosuppression with tacrolimus and rapamycin; other agents are used only with intolerance of tacrolimus and rapamycin. A 150 mg/m^2 dose of rituximab is administered on post-operative day one. For purposes of this study, only established immunosuppression was reported (not initial). Tacrolimus was used more often for maintenance in the no rejection and concordant pancreas/kidney categories. This may explain why the no rejection category used less mycophenolate; there was a non-significant increase in rapamycin use. Prednisone was used more often in the PA and KA categories.

Table 2 quantifies the HLA mismatch and PRA distributions in each acute rejection category. There were no statistically significant differences in total HLA mismatches, A, B, DR mismatches or PRA.

Acute rejection

A total of 23.8% of cases had an episode of rejection [8.7% pancreatic rejection alone (PA), 4.4% had concordant pancreas and kidney (PK) rejection, and 10.7% had kidney rejection alone(KA)]. Seven patients had repeat kidney rejections (1 within 1 month, 1 at 6 months, 1 at 7 months, 1 at 13 months and 1 after 3 years); four had failed kidney and pancreas grafts; one had failed kidney graft only. Only

Table 1 Demographics

	PA	KA	PK	No rejection	p value
Number of patients	22 (8.7)	27 (10.7)	11 (4.4)	192 (76.2)	n/a
White	20 (90.9)	23 (85.2)	11 (100)	168 (87.5)	0.7234
Male	16 (72.7)	15 (55.6)	5 (45.5)	120 (62.5)	0.4211
Year of Tx					
2003–2008	15 (68.2)	15 (55.6)	9 (81.8)	109 (56.8)	0.3189
2009–2014	7 (31.8)	12 (44.4)	2 (18.2)	83 (43.2)	
Tacrolimus	20 (90.9)	24 (88.9)	11 (100)	189 (98.4)	0.0205*
Mycophenolate	15 (68.2)	19 (70.4)	7 (63.6)	91 (47.4)	0.0424*
Azathioprine	0 (0)	2 (7.4)	0 (0)	7 (3.7)	0.6155
Rapamycin (Sirolimus)	10 (45.5)	7 (25.9)	3 (27.3)	94 (49.0)	0.0871
Prednisone	4 (18.2)	4 (14.8)	0 (0)	6 (3.1)	0.0058*

Values are frequencies (percentages), with p values from Fisher's Exact Tests, due to low cell counts. $p < 0.05$ is considered significantly different, indicating that proportions are not homogeneous across groups

Table 2 HLA and PRA Characteristics

	PA	KA	PK	No rejection	p value
HLA Mistmatch					
0	1 (4.8)	1 (3.9)	1 (9.1)	4 (2.1)	0.8559
1	0 (0)	1 (3.9)	0 (0)	2 (1.1)	
2	1 (4.8)	0 (0)	1 (9.1)	11 (5.8)	
3	1 (4.8)	5 (19.2)	1 (9.1)	28 (14.7)	
4	5 (23.8)	3 (11.5)	3 (27.3)	51 (26.8)	
5	9 (42.9)	10 (38.5)	4 (36.4)	62 (32.6)	
6	4 (19.1)	6 (23.1)	1 (9.1)	32 (16.8)	
Unknown	1 (4.6)	1 (3.7)	0 (0)	2 (1.0)	
HLA A					
0	2 (9.5)	3 (11.5)	2 (18.2)	30 (15.8)	0.9055
1	10 (47.6)	8 (30.8)	4 (36.4)	69 (36.3)	
2	9 (42.9)	15 (57.7)	5 (45.5)	91 (47.9)	
HLA B					
0	1 (4.8)	1 (3.9)	1 (9.1)	9 (4.7)	0.8698
1	5 (23.8)	9 (34.6)	2 (18.2)	60 (31.6)	
2	15 (71.4)	16 (61.5)	8 (72.7)	121 (63.7)	
HLA DR					
0	3 (14.3)	3 (11.5)	2 (18.2)	23 (12.1)	0.2961
1	5 (23.8)	11 (42.3)	7 (63.6)	71 (37.4)	
2	13 (61.9)	12 (46.2)	2 (18.2)	96 (50.5)	
PRA (class 1)					
0–30	21 (100)	23 (88.5)	9 (81.8)	181 (95.3)	0.0655
31–100	0 (0)	3 (11.5)	2 (18.2)	9 (4.7)	
PRA (class 2)					
0–30	20 (95.2)	25 (96.2)	11 (100)	183 (96.3)	0.8883
31–100	1 (4.8)	1 (3.9)	0 (0)	7 (3.7)	

Values are frequencies (percentages), with p values from Fisher's Exact Tests, due to low cell counts. $p<0.05$ is considered significantly different, indicating that proportions are not homogeneous across groups

one patient had repeat pancreas rejection (that was within 5 months); however, both pancreas and kidney grafts are still functioning.

72.2% of the kidney rejections were grade IA, 22.2% of the kidney rejections were grade IB, and 5.6% of the kidney rejections were grade IIA. 18.9% of the kidney rejections occurred within the first 6 months, 13.5% occurred between 6 and 12 months, 21.6% occurred between 1 and 5 years, and 45.9% of the kidney rejections occurred after 5 years. A characterization of the timing of pancreas rejections reveals 6% within the first 6 months, 27.3% occurred between 6 and 12 months, 27.2% occurred between 1 and 5 years, and 39.4% of the pancreas rejections occurred after 5 years.

91% of pancreas rejections were treated with solumedrol alone, with a 20% failure rate; 9% of pancreas rejections (three rejections) were treated with solumedrol followed by ATG, with one failure. 83.8% of kidney rejections were treated with solumedrol alone, with a 12.9% failure rate; 16.2% of kidney rejections (6 rejections) were treated with solumedrol followed by ATG, with one failure.

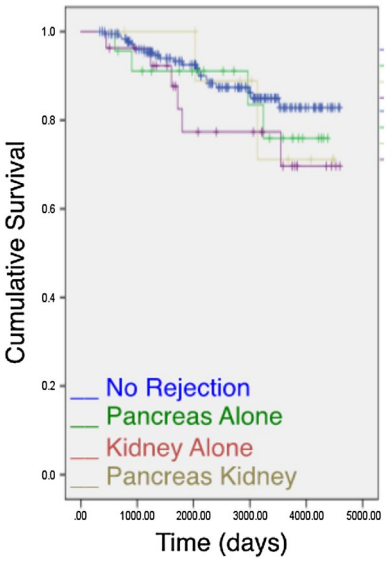

Fig. 1 Patient survival versus the four acute rejection categories. The log-rank test shows no difference between strata ($p=0.4149$). Rejection time is significantly associated with patient survival time, though. Cox proportional hazards models show a significant association, $p=0.0096$, with a hazard ratio of 0.689 (longer rejection time → longer survival time). Simple correlation analysis gives a correlation coefficient of 0.874 with $p=0.0002$

Patient survival by rejection category

Figure 1 displays patient survival according to rejection type for all patients. PA, KA, and PK did not have an adverse affect on patient survival ($p=0.562$, 0.713, 0.174 respectively). The log-rank test shows no difference between strata ($p=0.4149$). Time to Rejection is significantly associated with patient survival time however. Cox proportional hazards models show a significant association, $p=0.0096$, with a hazard ratio of 0.689. Late rejections (of any graft) are associated with superior patient survival. Correlation analysis gives a correlation coefficient of 0.874 with $p=0.0002$.

Kidney survival

Figure 2 displays kidney allograft survival according to rejection type for all patients. KA had an adverse impact on kidney survival as did PK ($p=0.002$, $p<0.0005$) but isolated pancreas rejection (PA) did not ($p=0.07$). Although the magnitude of adverse effect on kidney survival was greater for PK as compared to KA, we were unable to show statistical significance ($p=0.092$). Although visually there appears to be a 15% decrease in kidney graft survival with

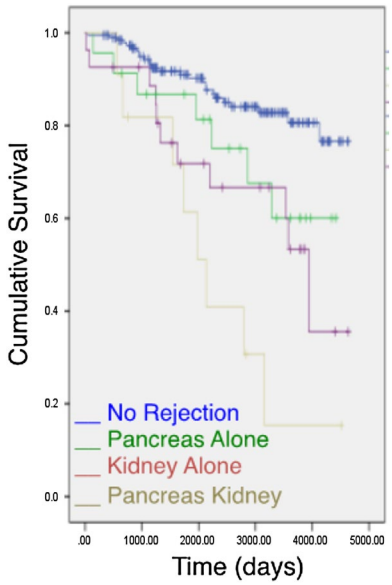

Fig. 2 Kidney Survival versus the four acute rejection categories. The log-rank test shows a significant difference between strata ($p < 0.0001$). PA is not associated with adverse kidney survival whereas PK and KA are. Rejection time is also significantly associated with patient survival time. Cox proportional hazards models show a significant association, $p < 0.0001$, with a hazard ratio of 0.686 (longer rejection time → longer kidney survival time). Simple correlation analysis gives a correlation coefficient of 0.858 with $p < 0.0001$

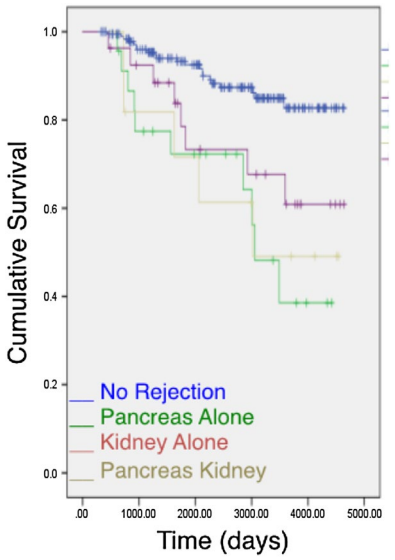

Fig. 3 Pancreas survival versus the four acute rejection categories. The log-rank test shows a significant difference between strata ($p = 0.0004$). PA, PK, and KA are all associated with adverse pancreas survival. Rejection time is also significantly associated with patient survival time. Cox proportional hazards models show a significant association, $p = 0.0005$, with a hazard ratio of 0.764 (longer rejection time → longer pancreas survival time). Simple correlation analysis gives a correlation coefficient of 0.804 with $p < 0.0001$

isolated pancreas rejection group, we were unable to show statistical significance; this may be due to small numbers.

Pancreas survival

As seen in Fig. 3, KA adversely affected pancreas survival ($p = 0.019$) although PA did not adversely affect kidney survival ($p = 0.07$). The deleterious effect of PA, PK, and KA on pancreas survival did not have intergroup statistical significance.

Patient survival by graft failure

As seen in Figs. 4 and 5, both pancreas allograft failure and kidney allograft failure had an adverse impact on patient survival ($p = 0.0487$). During the study period for our cohort, only one patient with a functioning kidney died; similarly, only one patient with a functioning pancreas died. Over the time course, half of the patients with kidney failure died; three quarters of the patients with pancreas failure died.

Creatinine, tacrolimus levels, HbA1c

Interestingly, PA, KA and PK were all associated with an increase in creatinine over time ($p = 0.0079$, <0.0001, 0.0006); however, we were unable to show any significant differences between the rejection categories suggesting that all are prone to chronic kidney disease (Fig. 6).

The authors used only the 12-h FK levels for the analysis. Figure 7 demonstrates non-significance between groups in tacrolimus levels over a 10 year period ($p = 0.4584$).

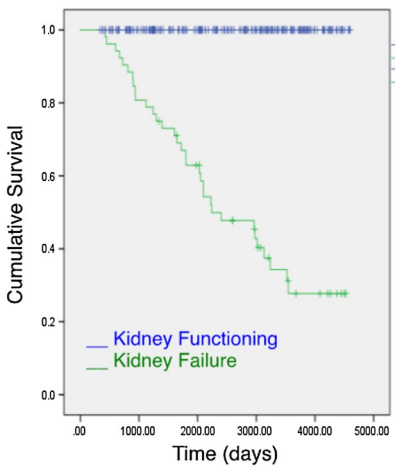

Fig. 4 Patient survival (time until death) with *kidney* status/failure. There is a significant difference between groups: log-rank test $p = 0.0487$. There is a significant association with rejection time: $p = 0.0236$ (Hazard Ratio = 0.717)

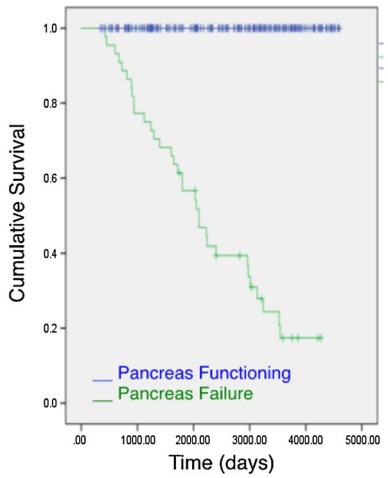

Fig. 5 Patient survival (time until death) with *pancreas* status/failure. There is a significant difference between groups: log-rank test p = 0.0487. There is a significant association with rejection time: p = 0.0236 (Hazard Ratio = 0.717)

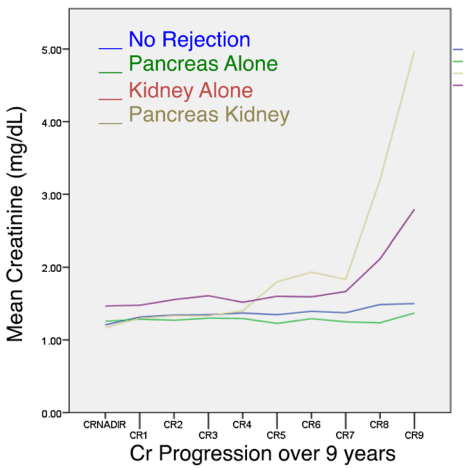

Fig. 6 For CR, there is a significant overall difference between groups over time (p < 0.0001). The "no rejection" group is significantly different from the "pancreas" group (p = 0.0079) and the "both" group (p = 0.0006) and the "kidney" group (p < 0.0001). These pairwise differences have been adjusted for multiple comparisons, to control for Type I error rate, using Tukey's adjustment

We were unable to demonstrate statistically significant differences in fasting glucose levels for PA, KA, and PK (p = 0.0850). However, Fig. 8 non-significantly documents that glucose control was most impaired in isolated pancreas rejection, only moderately impaired in PK and least impaired in KA. Consistent with the above observation, Fig. 9 demonstrates that Hba1c was elevated in PA as compared to KA or no rejection. There were no differences between KA and PK as compared to no rejection or between KA versus PK; this suggests that kidney rejections and concordant pancreas kidney rejections were more aggressively treated and better preserved pancreas function. However, we were unable to demonstrate statistical significance for HbA1c between PA and PK.

Discussion

This is a retrospective study of 252 SPK tranplants at a single center that examines the effect of clinically diagnosed rejection of the pancreas, kidney, or both on long-term graft and patient outcomes. Our center does not routinely implement pancreas biopsies to diagnose rejection; since we only perform enterically drained pancreas transplants, cystoscopic biopsies are not possible (as in bladder drained pancreata); percutaneous drainage can be technically challenging and operator dependent; there may be discordance with duodenal biopsies; and kidney biopsy cannot be used as a surrogate for pancreas biopsy. Clinical diagnosis and treatment of elevated lipase with CT abdomen, serum glucose, HbA1c and C-peptide has allowed for the exclusion of differential pancreas disorders and clinical diagnosis of pancreas rejection with treatment with steroids and/or ATG with resultant excellent graft and patient survival at our institution. Therefore, even though biopsy remains the gold standard (albeit a practically difficult and risky one), we believe that our SPK analysis for clarification of the nature of concordance (or discordance thereof) is valid and useful.

Also, the predominant immunosuppression at our institution is steroid-free, MTORI-containing with rituximab on post-op day one, which is unique and uncommon and is not generalizable to the field of pancreas transplantation. However, we believe it is the efficacy of immunosuppression and not the actual drugs used that contribute to the occurrence of graft rejection and the resultant concordance or discordance of the pancreas and kidney rejections. The pancreas transplantation experience at our institution has been previously reported; from 2003 to 2011, 1 year patient, pancreas and kidney allograft survival were 96, 91, and 94%, respectively with 7 day and 90 day graft loss rate of 4 and 6% respectively [16].

The significance of antibody-mediated rejection (AMR) of the kidney allograft in simultaneous pancreas-kidney transplantation is relatively unexplored. Pascual et al. reported in 2008 that the incidence of AMR of the kidney in SPK is 14%; 40% of AMR occur early and resolve with treatment and 60% occur late and triple the risk of kidney and pancreas allograft loss [17]. The majority of the studies of AMR and the role of DSA in pancreas transplantation have not done an isolated analysis of SPK transplants. Parajuli et al. report that, in SPK transplants, there is a high rate of discordance in rejection but, in some instances, there is

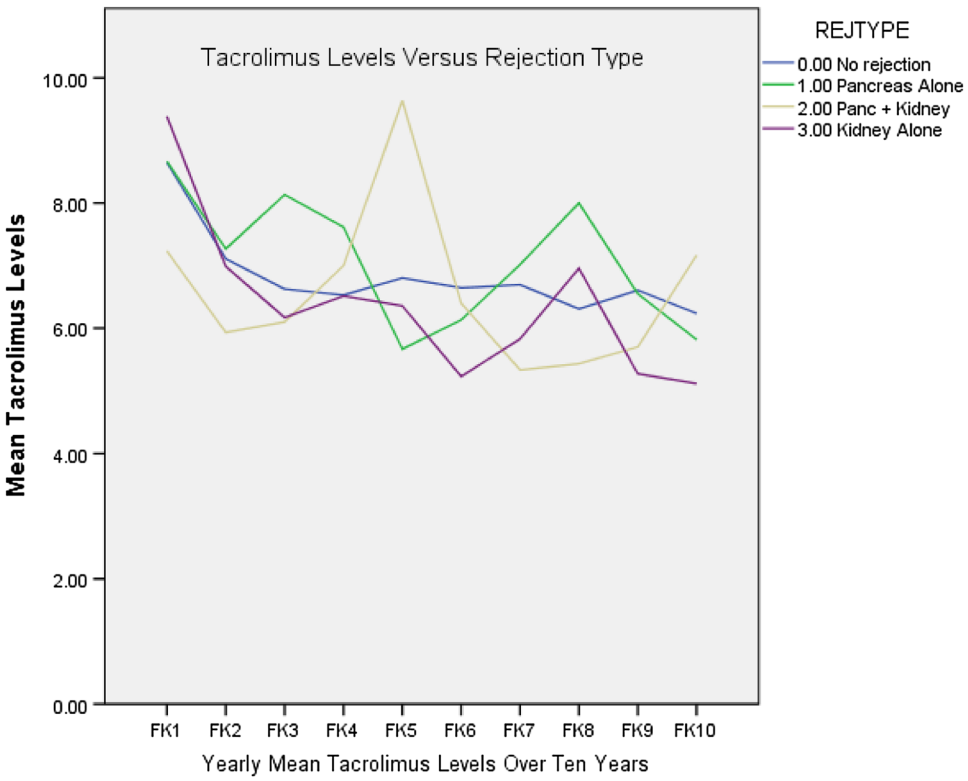

Fig. 7 For FK, there is *not* a significant overall difference between groups over time (p = 0.4584). There were no significant pairwise comparisons

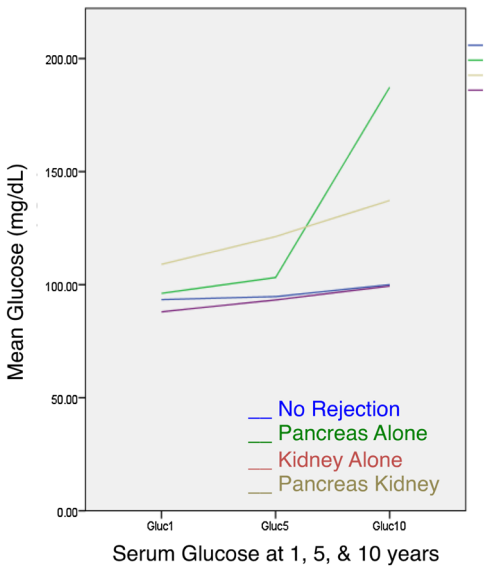

Fig. 8 For GLU, there is a *not* significant overall difference between groups over time (p = 0.0850). There were no significant pairwise comparisons

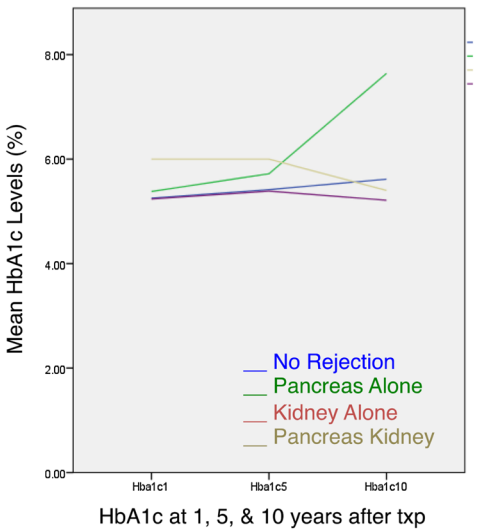

Fig. 9 For A1C, there is a significant overall difference between groups over time (p = 0.0016). The "pancreas" group is different from the "kidney" group (p = 0.0006) and the "pancreas" group is different from the "no rejection" group (p = 0.0349). These pairwise differences have been adjusted for multiple comparisons, to control for Type I error rate, using Tukey's adjustment

also discordance in type of rejection, i.e. AMR in one organ and ACR in the other [18].

A study of concordance requires uniformity of rejection type so that one can use available knowledge to promote a potent analysis of novel patient and graft survival data. The paucity of data on AMR in SPK makes inclusion of AMR in our study subject our data analysis to ambiguity and misinterpretation. Moreover, the fundamental assertion of our study was that in concordant rejection, the mechanism of injury to the kidney allograft and pancreas allograft

is the same. It was our desire to study the mechanism of T cell mediated graft injury and not antibody mediated graft injury. The optimal approach to the study of concordance in SPK necessarily involves the study of graft injury due to one mechanism, either cell-mediated or antibody-mediated. Discordance of type of rejection has not been studied and would require a large population of patients since the incidence is likely to be low.

A major limitation of this study is that 88% of the study population is Caucasian. This may limit the generalizability of this study. However, the advantage of the uniformity of race is that there is lesser variation in genetic, geographic and cardiovascular variables, which allows us to focus on the impact of rejection on graft and patient survival, rather than variables such as hypertension, atherosclerosis, and sensitization, which are more common in African Americans, for example.

Our study shows that PA rejection is not associated with decreased kidney survival and concordant dual organ PK rejection does adversely affect kidney survival. This suggests that pancreas rejections can be discordant. Since clinically concordant pancreas and kidney rejections are associated with an adverse effect on kidney survival, more frequent monitoring of creatinine in the year adjacent to a pancreas rejection may be indicated. Moreover, intensification of immunosuppression for a certain period of time up to a year after acute rejection of a pancreas or kidney graft may prolong the function of one or both grafts.

Not surprisingly, kidney alone (KA) rejections decreased pancreas allograft survival to an equal extent as PA and PK rejection. This may be due to the fact that immunosuppression that is not strong enough to protect a kidney from rejection is likely to have immunological injury to the pancreas as well. Hence, more frequent and vigilant monitoring of pancreas function in the year adjacent to a kidney rejection may be indicated; in this scenario, protocol biopsies of the pancreas may be the most effective method of monitoring the immunological status of the pancreas.

In addition, the authors analyzed the data by using adjustment for potential risk factors of mortality in diabetic kidney disease patients especially coronary artery disease risk factors (age, gender, hypertension, hyperlipidemia, hemoglobin A1c). We have adjusted the survival data with the above covariates in a Cox Hazard model. None of the covariates were significantly associated in the survival analyses, nor did they attenuate the main result. All of the SPK patients were non-smokers or quit smoking before SPK transplantation; the majority remained non-smokers after transplantation over the long term; however, smoking status after transplantation has not been strictly documented and could not be used for adjustment of the survival data. There was no difference in progression of CKD amongst PA, KA and PK. Additionally, the incidence of delayed graft function at our institution is very low; nevertheless, serum creatinine at week 1 did not alter the survival analyses.

We did not see any difference in fasting serum glucose levels between the four rejection categories. This substantiates the notion that hyperglycemia is a poor or late marker for gauging pancreas function. Long-term HbA1c was however worse in PA than KA or no rejection. Lack of progression of HbA1c in KA or PK suggests protection of pancreatic function due to aggressive immunosuppression.

Kaplan et al. [13] reported poor kidney outcomes in isolated pancreas rejection; however, they only looked at rejections that occurred in the first year post-transplantation. Moreover, since they looked at UNOS/OPTN data, they do not have data on tacrolimus levels, immunosuppression protocols, and data on serum glucose, HbA1c, and serum creatinine. Moreover, the study didn't differentiate between subclinical and clinically concordant pancreas and kidney rejections.

In SPK, since both the pancreas and kidney grafts are from the same donor, it is immunologically plausible that pancreas rejections should beget kidney rejections and vice versa. However, the pancreas is more immunogenic; it is suggested that pancreas grafts are associated with stronger affinity for and homing of immune cells. It is also suggested that bowel grafts are less resistant to rejection than pancreas grafts; similarly, pancreas grafts are less resistant to rejection than kidney grafts [19]. Hence, rejection tends to be sequential; bowel grafts reject first followed by pancreas grafts and kidney grafts are the last to reject. We suggest that in the clinical management of SPK, the bowel/pancreas grafts reject first and this is clinically treated aggressively leading to the cessation of the immune process prior to involvement of the kidney graft. Hence, it is possible to have a pancreas rejection that occurs in the absence of kidney rejection. However, concordance likely does play a role in SPK transplants and, therefore, dual or concordant rejection should be the most deleterious.

Our data suggests that graft rejection episodes are not associated with poorer patient survival. This may be because of aggressive treatment of rejection and because the overall incidence of rejection was low. Moreover, it seems poor patient survival is associated not with graft rejection but primarily with graft loss.

Limitations of this study include the following: the study is retrospective; the study is single center; some of the groups have small numbers; issues such as compliance and other clinical events such as BK, CMV, and PTLD may have impacted the course of the graft loss. We also did not capture the data regarding the types of treatment given for individual rejection episodes. Nevertheless, all patients were treated for either organ rejection according to standard treatment clinical criteria based on the clinical condition of the graft

and patient. Most pancreas transplants were not biopsied and were treated on the basis of elevation of enzymes or glucose.

A major limitation of this study is that 88% of the study population is Caucasian. This may limit the generalizability of this study. However, the advantage of the uniformity of race is that there is lesser variation in genetic, geographic and cardiovascular variables, which allows us to focus on the impact of rejection on graft and patient survival, rather than variables such as hypertension, atherosclerosis, and sensitization, which are more common in African Americans, for example. Our SPK population, however, is ethnically similar to the global SPK population. It is the kidney transplantation population in the United States that certainly includes a higher proportion of African Americans.

In conclusion, it is immunologically plausible that pancreas rejections and kidney rejections should be concordant. However, because the pancreas is more immunogenic, is less resistant to rejection, and rejects earlier than the kidney, aggressive treatment of pancreas rejections leads to cessation of the immune process prior to involvement of the kidney graft. Hence, isolated and discordant pancreas rejections do occur and they are not associated with adverse kidney graft survival.

Compliance with ethical standards

Conflict of interest None of the authors have any conflicts of interest to disclose.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study formal consent is not required.

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