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Allograft outcomes after simultaneous pancreas kidney transplantation comparing T1DM with Type 2 DM (detectable C-peptide and absence of glutamic acid decarboxylase 65 antibody)

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Abstract

Background—Prior studies reporting outcomes after pancreas transplant have included a combination of C-peptide cutoffs and clinical criteria to classify type 2 diabetes mellitus (T2DM). However, since the kidney is the major site for C-peptide catabolism, C-peptide is unreliable to discriminate type of diabetes in patients with kidney disease.

Methods—To improve the discriminating power and better classify type of diabetes we used a composite definition to identify T2DM: Presence of C-peptide, negative GAD65 antibody, absence of diabetic ketoacidosis and use of oral hypoglycemics. Additionally, BMI <30 kg/m2 and use of < than 1 unit/kg of insulin/day are selection criteria among T2DM patients with ESRD deemed suitable for SPKTx. We compared graft and patient survival between T1DM and T2DM after SPKTx.

Results—Our study cohort consisted of 80 patients, 10 of whom were assigned as T2DM based on our study criteria. Approximately 15% of patients with T1DM had detectable C-peptide. Cox regression survival analyses found no significant differences in allograft (pancreas and kidney) and patient survival in the 2 groups. The mean creatinine clearance at 1 year by MDRD equation was not significantly different between the 2 groups. Among those with 1 year follow up, all patients with T2DM had HbA1C < 6.0 at 1 year vs. 92% of those with T1DM.

Conclusion—SPKTx needs to be considered in the therapeutic armamentarium for renal replacement in selected patients with T2DM and ESRD. Utilization of C-peptide in patients with ESRD as sole criteria to phenotype type of diabetes can be misleading.

Background

Simultaneous pancreas and kidney transplantation (SPKTx) is a well accepted therapeutic option for patients with Type 1 DM (T1DM) and ESRD. However, there is no consensus

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with respect to performing SPKTX among patients with type 2 diabetes mellitus (T2DM) with end-stage renal disease (ESRD). Nevertheless, approximately 5-10% of all SPK transplants reported to the SRTR are performed in patients with T2DM and ESRD. Prior studies have reported comparable outcomes in improvement in quality of life and allograft and patient survival among patients with T2DM similar to patients withT1DM receiving SPKTx.[1-4]

Assigning a type of diabetes to an individual with ESRD becomes challenging due to the alteration in the insulin and glucose metabolism in patients with kidney disease, and many diabetics do not strictly fit into one class. Since there are no absolute established diagnostic criteria to assign a type of diabetes, individual centers have used their discretion in adopting criteria in the labeling of a patient as T2DM. Prior reports have included a combination of C-peptide cutoffs – C-peptide >0.8 ng/mL,[2] C-peptide >2 ng/mL[5] and clinical criteria based on American Diabetes Association and World Health Organization guidelines. However, since the kidney is the major site for C-peptide catabolism and excretion,[6-10] the utilization of C-peptide alone to phenotype diabetes in patients with ESRD is imprecise. To improve the discriminating power and better classify type of diabetes in patients with ESRD, we chose a composite criterion including clinical criteria, C-peptide assay and autoimmune response to pancreatic β-cell – by measuring antiglutamic acid decarboxylase (anti-GAD 65) antibodies and compared outcomes between T1DM and T2DM after SPKTx.

Methods

After Institutional Review Board approval, we conducted a retrospective observational study to compare recipient and donor characteristics in addition to allograft (kidney and pancreas) and patient survival after SPK transplant between T2DM vs. T1DM. We used the following composite definition to identify T2DM: Presence of C-peptide, negative GAD65 antibody, absence of diabetic ketoacidosis and use of oral hypoglycemics during the course of disease. Additionally, BMI <30 and use of < than 1 unit/kg of insulin/day were also used in selecting T2DM patients for SPKTx. Patients designated as T1DM included those with early onset of disease, requirement of insulin from onset and/or presence of diabetic ketoacidosis. All patients received deceased donor organs and were enteric drained. Immunosuppression included induction with r-ATG (total dose 6 mg/kg) or Campath (30 mg single dose) and maintenance with tacrolimus, mycophenolic acid and rapid steroid taper (off steroids by postoperative day 4). Patients with positive crossmatch received steroid long-term. Functioning kidney allograft was defined as not being retransplanted and not being on dialysis for renal support. Functioning pancreas allograft was defined as normal HbA1c, fasting blood glucose and insulin independence.

Results

Our study cohort consisted of 80 patients who received SPKTx between October 2003 and September 2008 without immediate technical complications – of whom 10 were assigned as T2DM based on study criteria. Median range of follow-up was 485 days. Table 1 describes our cohort. A T2DM were older and non white. Approximately 87% of T1DM were white in comparison to only 30% of those with T2DM. Mean duration of diabetes pre-transplant was greater in T1DM in comparison to the T2DM. Approximately 15% of patients with T1DM had detectable C-peptide. The reference range for C-peptide in our laboratory is (between 0.5 – 3.3 ng/mL). Cox regression survival analyses found no significant differences in allograft (pancreas and kidney) and patient survival in the 2 groups. The mean creatinine clearance by MDRD equation was not significantly different between the 2 groups. All (100%) patients with T2DM had HbA1C <6.0 at 1 year in comparison to approximately 96% of those with T1DM (Table 2).

Discussion

With the increasing epidemic of T2DM, the prevalence of (ESRD) due to diabetes mellitus has risen from 15% in 1980 to 45% in 2000[11] and this is expected to double in the next decade.[12] Given the limited supply of usable donor pancreata, it is imperative to define the optimal T2DM patient (i.e. patient with minimal insulin resistance) who would benefit from a combination of pancreas transplant at the time of kidney transplant.

Several studies in populations with normal kidney function have shown C-peptide concentrations to be useful in discriminating T1DM from T2DM.[13-15] However, since C-peptide is cleared by the kidney, using C-peptide as the sole criteria is not reliable to discriminate type of diabetes in patients with ESRD since some patients with T1DM and ESRD will have persistent C-peptide concentrations.[16] Diabetics with ESRD show a several fold higher C-peptide concentration compared to diabetics without renal impairment.[17,18] Additionally, C-peptide concentrations have been shown to be elevated in non-diabetic patients[8] and animals[19] with ESRD. Utilization of C-peptide alone will cause misclassification of diabetes in patients with ESRD. In our study we had 15% of patients with T1DM with detectable C-peptide. Additionally, all patients with T2DM had detectable C-peptide ranging from 0.3 ng/mL – 8.1 ng/mL. Based on prior studies a cut-off of C-peptide > 0.8 ng/mL[2] we would have misclassified approximately 8% of the T1DM as T2DM. Similarly utilization of C-peptide cut offs >2.0 ng/mL for classifying T2DM[5] we would have classified 30% of our T2DM as T1DM.

At our center, the rationale for our selection criteria (including both certain clinical criteria and biochemical markers) was to select the “optimal T2DM” - one who does not demonstrate significant insulin resistance (BMI cut off for T2DM is 30 Kg/m2 and less than 1 unit/Kg insulin requirement). Prior studies have observed higher technical pancreas allograft failure in patients with BMI above 30 Kg/m2.[20] Additionally, there is a reportedly significantly higher incidence of new-onset hyperglycemia despite presence of a functioning graft among pancreas recipients with higher pretransplant BMI and higher pretransplant insulin requirements (post-transplant diabetes mellitus after pancreas transplantation.[21] Our results using our selection criteria have demonstrated comparable outcomes among T2DM and T1DM receiving SPKTx. However, these results need to be validated in larger cohort of patients with long-term follow up.

In conclusion, since outcomes among “select” T2DM with ESRD are comparable to reported outcomes of SPKTx in T1DM with ESRD, SPKTx needs to be considered in the therapeutic armamentarium for renal replacement in selected patients with T2DM. The challenge lies in defining criteria to identify the subset of patients with T2DM who will benefit from SPK transplant. Perhaps a composite selection criteria needs to be adopted including clinical criteria and biochemical markers (C-peptide and insulin antibodies) to discriminate type of diabetes in patients with ESRD to determine who would benefit most from SPK transplant, thus best utilize the limited organ supply.

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Table 1
Descriptive Analysis of the Study Cohort

	T1DM, N=70	T2DM, N=10
Mean age at transplant*	44 +/- 11	51+/- 9
Race		
% White	87	30
% African American	1.5	10
% Hispanic	10	30
% Native American**	1.5	20
% Asian	0	10
% male*	88	90
BMI (kg/m2) mean +/- SD*	24.8 +/- 4.2	27 +/- 3
Age of DM onset (years) mean +/- SD **	15 +/- 9.4	30 +/- 10.1
Duration of DM pre-transplant (years) mean +/- SD **	29 +/- 9	19 +/-10
% documented retinopathy**	85	50
% documented neuropathy*	60	80
% documented autonomic dysfunction*	50	50

* P value: not significant,

** P value <0.01

Table 2

Outcomes after SPKTx in Study Cohort

Outcomes	T1DM	T2DM
Clinical acute kidney rejection, % + ve	10	30
Clinical acute pancreas rejection, % + ve	15	10
% with mean HbA1C > 6.0 at 1 months	38	20
% with mean HbA1C > 6.0 at 12 months *	8	0
CrCl 1 month (MDRD equation) Mean +/-SD	69 +/- 25	60 +/- 12
CrCl 12 month (MDRD equation) Mean +/- SD *	68 +/- 24	69 +/- 22

* patients with >/=1 year follow-up