Retrospective Assessment of Islet Cell Autoantibodies in Pancreas Organ Donors

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OBJECTIVE — Of deceased pancreas donors, 3–4% may have autoantibodies (AAb) to pancreatic islet cell antigens; these autoantibodies are well-established markers of type 1 diabetes. We investigated whether donor AAb positivity could affect the outcome of pancreas transplantation.

RESEARCH DESIGN AND METHODS — We retrospectively tested AAb in 135 donors whose pancreata and kidneys were transplanted in type 1 diabetes patients. We measured AAb to glutamic acid decarboxylase (GAD-AAb), the tyrosine-phosphatase-like protein IA2 (IA2-AAb), and insulin (insulin-AAb). We then evaluated pancreas transplant outcome data.

RESULTS — Four of 135 (2.96%) donors were AAb positive: three donors had GAD-AAb, and one donor had insulin-AAb. Their respective recipients became insulin independent on follow-up. Three of the four recipients had normal, insulin-producing grafts 3–5.8 years after transplant. The recipient of the insulin-AAb–positive donor pancreas developed chronic rejection following discontinuation of immunosuppression 3.3 years after transplant.

CONCLUSIONS — Single AAb positivity did not affect the outcome of pancreas transplantation in our study.

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Type 1 diabetes is an autoimmune disease resulting in β-cell loss and insulin dependence (1). Autoantibodies (AAb) to several islet antigens are predictive and diagnostic for type 1 diabetes (2). The presence of multiple AAb correlates with higher disease risk in first-degree relatives (3). Simultaneous kidney-pancreas (SPK) transplantation is therapeutic for type 1 diabetic patients with end-stage renal disease (4). Studies suggest that 3–4% of organ donors have at least one AAb to islet cell antigens (5,6). It is not known whether AAb positivity could be a donor-related factor affecting the outcome of pancreas transplants. We performed retrospective AAb testing in 135 deceased donors whose pancreata and kidneys had been transplanted in type 1 diabetic patients and then verified clinical outcome.

RESEARCH DESIGN AND METHODS

We have performed 350 SPK transplants over the past 18 years in type 1 diabetic patients with end-stage renal disease. Type 1 diabetes diagnosis is routinely verified by lack of detectable C-peptide after a sustacal challenge. All pancreas transplants are bladder drained (7). We retrospectively tested AAb in 135 donors (90 male and 45 female). The mean age was 25.8 years (range 1.9–51). Pancreata and kidneys from the tested donors were transplanted into type 1 diabetic patients between 1998 and 2005. We measured AAb to glutamic acid decarboxylase (GAD-AAb), the tyrosine-phosphatase-like protein IA2 (IA2-AAb), and insulin (insulin-AAb) using standard radioimmunoassays. AAb levels are expressed as index levels calculated from the counts per minute of the test sample and the positive and negative control samples. Receiver operating curves identified assay cutoffs of 11.44, 3.72, and 6.85 for the GAD, IA2, and insulin AAb assays, respectively. Our laboratory participated in the Diabetes Autoantibody Standardization Program of the Immunology of Diabetes Society and Centers for Disease Control in 2000, 2002, 2003, and 2005 (8). Donors and recipients were HLA typed using standard serology. The institutional review board of the University of Miami School of Medicine approved the study.

RESULTS

Four of 135 (2.96%) donors were AAb positive: three donors had GAD-AAb, and one donor had insulin-AAb. Donors with GAD-AAb had low AAb levels. Donor 4 had markedly elevated insulin-AAb levels. No donor had IA2-AAb or multiple AAb. Tables 1 and 2 show the characteristics of the AAb-positive donors and corresponding recipients. Two donors with GAD-AAb were homozygous for the HLA-DR4 or -DR3 susceptibility alleles; the remaining GAD-AAb–positive donor carried a presumably protective HLA-DR2. The donor with insulin-AAb had neutral HLA types.

We then evaluated outcome data from the respective recipients. Our SPK recipients had a mean ± SD follow-up of 5 ± 2.1 years. All patients transplanted with a pancreas from a single AAb-positive donor became insulin independent; three-fourths of the patients transplanted with a pancreas from an AAb-positive donor had normal, insulin-producing grafts 3–5.8 years after transplant (Table 2). The recipient of the pancreas from GAD-AAb–positive donor 1 had a pancreas transplant biopsy 3.2 years after transplantation showing no β-cell loss, insulitis, or other abnormalities. This recipient had elevated GAD-AAb levels preceding the transplant that

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Table 1—*Age distribution and HLA-DR types of pancreas donors*

Age-group (years)	*n*	Non-DR3/4	DR3/X	DR4/X	DR3/4
≤10	7	2	3	2	0
11–20	43	24	11	7	1
21–30	36	23	5	7	1
31–40	35	19	4	12	0
41–50	14	7	3	3	1
Total	135	75	26	31	3

persisted essentially unchanged during follow-up. The recipient of the pancreas from insulin-AAb–positive donor 4 developed chronic rejection following discontinuation of immunosuppression 3.3 years after transplant. At that time, GAD-AAb were transiently positive. The patient returned to insulin dependency despite maintaining residual C-peptide secretion for up to 2.2 years after developing chronic rejection. The patient's last C-peptide level was 2.3 ng/ml. Loss of graft function did not differ among recipients of AAb-positive and AAb-negative donors (1 of 4 vs. 12 of 131; $P = 0.33$).

CONCLUSIONS — There is interest in screening pancreas donors for autoantibodies to identify pre-diabetic donor pancreata that may not be suitable for transplantation and could be made available for research (5). The Juvenile Diabetes Research Foundation is supporting large-scale screening to identify AAb-positive pancreas donors for research (www.jdrfnpod.org). A recent analysis of pancreas donors aged 25–60 years from the general population showed that single AAb positivity is not commonly associated with insulitis and β-cell loss, via analyzing ~0.5 cm^3 bioptic fragments of pancreata that were used for islet cell isolation (6). Insulitis was found in only two donors who were positive for 3 AAb and not in 59 donors positive for 1–2 AAb.

We identified four donors with a single AAb, consistent with the reported frequency in organ donors (5). Our data include subjects younger than those in previous studies (5,6): of our donors, 55% were aged <25 years, an age-group with higher type 1 diabetes incidence. Indeed, this group yielded three of the four AAb-positive donors. Our analysis is unique in providing transplant outcome data from patients who received a pancreas from a single AAb-positive donor. All patients became insulin independent on follow-up. In a patient who continued to be euglycemic, a biopsy performed 3 years after transplantation did not evidence islet damage. The recipient of the insulin-AAb–positive donor pancreas lost transplant function due to chronic rejection related to noncompliance. Overall, our outcome data are consistent with biopsy data from previous studies showing that single AAb positivity may not always be associated with clinically significant autoimmunity and β-cell damage in organ donors (5,6). The findings are consistent with the low diabetes risk associated with single AAb positivity in the general population (9,10). Relevant to clinical pancreas transplantation, our data suggest that single autoantibody positivity is unlikely to affect pancreas transplant outcome and may help to refine strategies for ongoing pancreas donor AAb-screening initiatives, of which we remain strong supporters. Limited access to human pancreata with ongoing autoimmunity remains a major obstacle to the advancement of our understanding of human type 1 diabetes.

Table 2—*AAb status, age, HLA types, and clinical outcome data for AAb-positive donors and respective recipients*

	Donors				Recipients					
	Positive AAb	Index levels	Age (years)	HLA	Clinical outcome	Follow-up (years)	Age (years)	HLA	GAD-AAb	IA2-AAb
1	GAD	18	41	DR4/4	NGT	4.4	48	DR3/4	Positive	Positive
2	GAD	19.9	22	DR1/2	NGT	3	38	DR3/4	Negative	Negative
3	GAD	19.3	5	DR3/3	NGT	5.8	39	DR3/7	Positive	Positive
4	Insulin	162	19	DR6/7	PCR	6.8	44	DR1	Positive*	Negative

*SPK recipient 4 expressed GAD-AAb transiently following chronic rejection. NGT, normal glucose tolerance; PCR, pancreatic chronic rejection.

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