Ten Years of Preserved Kidney Function After Islet Transplant Graft Failure

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Several studies in patients with type 1 diabetes have examined the impact of islet transplantation (ITx) on renal function (1–3). Our group and others (1,4) have reported the beneficial effect of ITx. Equally relevant, however, is the assessment of renal function in patients with graft failure (GF) who are exposed to the well-known potential toxicity from immunosuppressive drugs and risk of development or progression of diabetic nephropathy related to unstable glycemic control (5). In this study, we examined the renal function of 12 recipients of allogeneic ITx who developed GF (stimulated C-peptide $<$0.3 ng/mL) but had at least 1 year (range 1.0–5.1) of graft function. Maintenance immunosuppression consisted of sirolimus and tacrolimus, which were discontinued after GF. Patients were enrolled in the ongoing Long Term Surveillance of Islet Transplant Recipients Following Complete Graft Loss study at the University of Miami, 6.0 $\pm$ 1.8 years (range 2.9–8.8) after GF. In this interim report, we provide data on renal function for a mean of 10.7 years after islet GF (Fig. 1*A*). The estimated glomerular filtration rate (eGFR) at the end of follow-up was comparable to eGFR at time of GF (86.0 $\pm$ 21.1 vs. 88.3 $\pm$ 21.8 mL/min/1.73 m^2; $P = 0.95$ after comparison of all study time points) (Fig. 1*B*). The rate of eGFR decline, variable among individuals, was not significantly different after immunosuppression discontinuation (0.5 $\pm$ 0.9 and 0.1 $\pm$ 1.0 mL/min/1.73 m^2/year after ITx and GF, respectively; $P = 0.35$) (Fig. 1*C*). By contrast, microalbuminuria (urine albumin–creatinine ratio 30–299 mg/g Cr) was observed in 2/12 (16.6%) subjects at ITx, 3/12 (25%) at half-graft survival, 5/12 (41.7%) at GF, and 1/11 (9.0%) at the last follow-up visit (Fig. 1*D*). None had macroalbuminuria. Four of the five subjects with microalbuminuria at GF had resolution after discontinuation of immunosuppression ($P = 0.0007$). One subject continued to have microalbuminuria, but this initially appeared at GF. Two subjects with preexisting microalbuminuria and resolution after immunosuppression discontinuation were switched from tacrolimus to mycophenolate mofetil while having graft function because of tacrolimus toxicity. HbA_{1c} improved following ITx and worsened after GF, despite reintroduction of insulin therapy, but was not significantly different throughout follow-up. Overall, we did not observe any association between proteinuria and renal function at time of ITx, blood pressure, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (3/5 subjects with microalbuminuria), or immunosuppression drug levels. We recognize that limitations of this study include the small sample size, a selection bias because inclusion criteria for ITx required an eGFR $>$60 mL/min/1.73 m^2 (in one case the eGFR was 55), and lack of a control group to better address the association between immunosuppression and albuminuria. Nevertheless, in this patient population, the eGFR was not compromised during the 10-year follow-up after occurrence of islet GF and microalbuminuria regressed after discontinuation of immunosuppression in four out of five subjects. The careful selection of islet recipients, improvement of metabolic control during graft function, management of risk factors, and withdrawal of calcineurin inhibitor therapy may be responsible for stabilization of kidney function.

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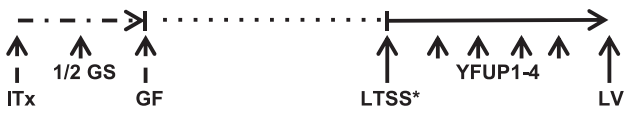
E.P. and F.V. contributed equally to this work.

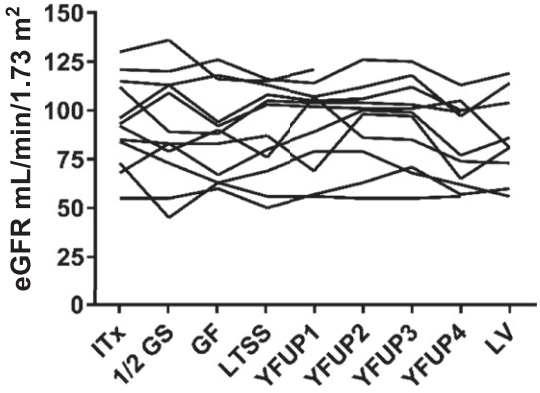
A

Demographic and clinical characteristics	
n	12
Sex, male (%)	6/12 (50)
Race, white (%)	12/12 (100)
Age, years , mean ± SD	40.2 ± 9.7
BMI (kg/m^2)	24.7 ± 2.5
Type 1 diabetes duration, years , mean ± SD	25.6 ± 14.3
Number of islet infusions	1.9 ± 1.0
Transplanted islet equivalent per kg, mean ± SD	7,955 ± 2,517
Macrovascular disease	
Cardiovascular disease (%)	2/12 (16.6)
Microvascular disease	
Retinopathy (%)	5/12 (41.6)
Nephropathy (%)	2/12 (16.6)
Peripheral neuropathy	0/12 (0)
Study time points (years, mean ± SD)	
ITx to 1/2 GS	1.4 ± 0.8
ITx to GF	2.8 ± 1.6
ITx to LTSS	8.7 ± 0.8
ITx to LV	13.4 ± 1.2
GF to LTSS	6.0 ± 1.8
GF to LV	10.7 ± 2.1



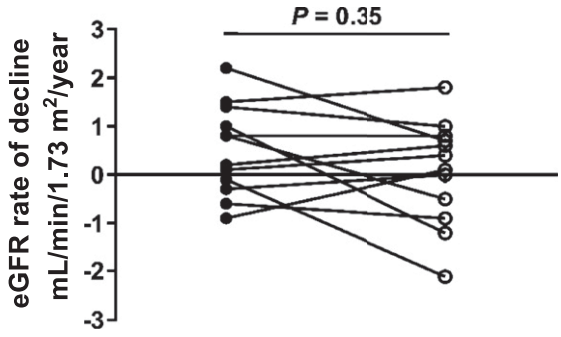
*One patient was lost to follow-up 1.7 years after enrollment; for 2 subjects the last visit on follow-up corresponded to the yearly follow-up visit 4.

B



ITx	93.7 ± 21.6 (92.5, 55-130)	*P* = 0.95
½ GS	91.5 ± 26.1 (86.0, 45-136)	
GF	88.3 ± 21.8 (89.0, 60-126)	
LTSS	89.8 ± 22.5 (95.0, 50-116)	
YFUP1-4	90.6 ± 21.4 (89.0, 55-126)	
LV	86.0 ± 21.1 (81.0, 56-119)	

C



D

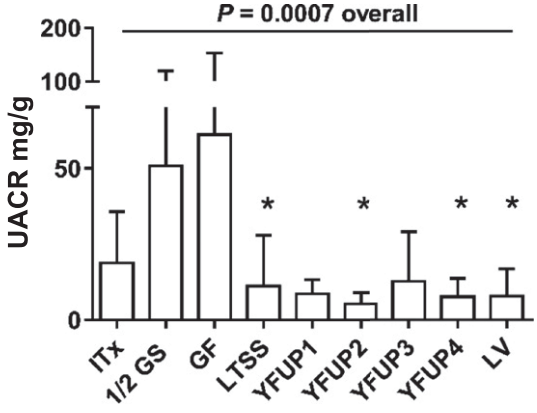


Figure 1—*A*: Demographic and clinical features of study subjects and study time points. The half-life graft survival (1/2 GS) provided information about renal function between ITx and GF. Data are presented as *n* (%) and mean ± SD. GF, graft failure; ITx, islet transplant; LTSS, enrollment in the long-term surveillance study; LV, last visit on follow-up; YFUP1-4, yearly follow-ups 1–4; the half-life graft survival provided information about renal function between ITx and GF. *B*: Renal function at the time of ITx, GF, study enrollment, and follow-up. The eGFR was calculated based on the Chronic Kidney Disease Epidemiology Collaboration equation. Data were analyzed using the Kruskal-Wallis test and presented as mean ± SD, median and range. *C*: Rate of decline of the eGFR. Each circle represents an ITx recipient; solid circles symbolize the changes in eGFR at ITx vs. last visit follow-up, and open circles symbolize the changes in eGFR at GF vs. last visit follow-up. Data were analyzed using the Mann-Whitney *U* test. *D*: Albumin excretion. Albuminuria was determined by the urine albumin–creatinine ratio (UACR) from first morning spot urine samples. Data were analyzed using the Kruskal-Wallis test. Data are presented as mean ± SD. *Significant *P* values vs. GF after Dunn's test correction for multiple comparisons.

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References

1. Fiorina P, Folli F, Zerbini G, et al. Islet transplantation is associated with improvement of renal function among uremic patients with type I diabetes mellitus and kidney transplants. J Am Soc Nephrol 2003;14:2150–2158
2. Shapiro AM. Islet transplants and impact on secondary diabetic complications: does C-Peptide protect the kidney? J Am Soc Nephrol 2003;14: 2214–2216
3. Thompson DM, Meloche M, Ao Z, et al. Reduced progression of diabetic microvascular complications with islet cell transplantation compared with intensive medical therapy. Transplantation 2011;91:373–378
4. Barton FB, Rickels MR, Alejandro R, et al. Improvement in outcomes of clinical islet transplantation: 1999-2010. Diabetes Care 2012;35: 1436–1445
5. Maffi P, Bertuzzi F, De Taddeo F, et al. Kidney function after islet transplant alone in type 1 diabetes: impact of immunosuppressive therapy on progression of diabetic nephropathy. Diabetes Care 2007;30:1150–1155