

Long-Term Beneficial Effect of Islet Transplantation on Diabetic Macro-/Microangiopathy in Type 1 Diabetic Kidney-Transplanted Patients

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OBJECTIVE — Our aim was to evaluate the long-term effects of transplanted islets on diabetic macro-/microangiopathy in type 1 diabetic kidney-transplanted patients.

RESEARCH DESIGN AND METHODS — A total of 34 type 1 diabetic kidney-transplanted patients underwent islet transplantation and were divided into two groups: successful islet-kidney transplantation (SI-K; 21 patients, fasting C-peptide serum concentration >0.5 ng/ml for >1 year) and unsuccessful islet-kidney transplantation (UI-K; 13 patients, fasting C-peptide serum concentration <0.5 ng/ml). Patients cumulative survival, cardiovascular death rate, and atherosclerosis progression were compared in the two groups. Skin biopsies, endothelial dependent dilation (EDD), nitric oxide (NO) levels, and atherothrombotic risk factors [von Willebrand factor (vWF) and D-dimer fragment (DDF)] were studied cross-sectionally.

RESULTS — The SI-K group showed a significant better patient survival rate (SI-K 100, 100, and 90% vs. UI-K 84, 74, and 51% at 1, 4, and 7 years, respectively, $P = 0.04$), lower cardiovascular death rate (SI-K 1/21 vs. UI-K 4/13, $\chi^2 = 3.9$, $P = 0.04$), and lower intima-media thickness progression than the UI-K group (SI-K group: $\Delta 1-3$ years $-13 \pm 30 \mu\text{m}$ vs. UI-K group: $\Delta 1-3$ years $245 \pm 20 \mu\text{m}$, $P = 0.03$) with decreased signs of endothelial injury at skin biopsy. Furthermore, the SI-K group showed a higher EDD than the UI-K group (EDD: SI-K $7.8 \pm 4.5\%$ vs. UI-K $0.5 \pm 2.7\%$, $P = 0.02$), higher basal NO (SI-K 42.9 ± 6.5 vs. UI-K $20.2 \pm 6.8 \mu\text{mol/l}$, $P = 0.02$), and lower levels of vWF (SI-K 138.6 ± 15.3 vs. UI-K $180.6 \pm 7.0\%$, $P = 0.02$) and DDF (SI-K 0.61 ± 0.22 vs. UI-K $3.07 \pm 0.68 \mu\text{g/ml}$, $P < 0.01$). C-peptide-to-creatinine ratio correlated positively with EDD and NO and negatively with vWF and DDF.

CONCLUSIONS — Successful islet transplantation improves survival, cardiovascular, and endothelial function in type 1 diabetic kidney-transplanted patients.

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Abbreviations: DBP, diastolic blood pressure; DDF, D-dimer fragment; eCNs, endothelial constitutive nitric oxide synthase; EDD, endothelial dependent dilation; IMT, intima-media thickness; SBP, systolic blood pressure; SI-K, successful islet-kidney transplantation; UI-K, unsuccessful islet-kidney transplantation; vWF, von Willebrand factor.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Islet transplantation, particularly after kidney transplantation, is an alternative to pancreas transplantation to restore endogenous insulin secretion (1–7). Islet transplantation is a safe procedure leading to an improvement of glycometabolic control and of protein and lipid metabolism (1,3,6–8). The benefits of the improvement of glycometabolic control alone on macroangiopathy are unknown (9,10).

Patients with type 1 diabetes are at high risk for several cardiovascular disorders, such as coronary artery disease, stroke, peripheral arterial disease, cardiomyopathy, and congestive heart failure (11). These risks are particularly high in patients with uremia and type 1 diabetes, even after kidney transplantation (12). A worsening of carotid lesion has been observed in patients undergoing kidney-alone transplantation (13). High levels of von Willebrand factors (vWF) and D-dimer fragments (DDFs), and impaired endothelial-dependent dilation (EDD) are commonly involved in development of atherosclerosis (14). In particular, endothelium modulates platelet adhesion, macrophage migration, lipid transport, and mitogenesis (14). Impairment of dilation ability is an important predictor of atherosclerosis and cardiovascular events (13,14). Both diabetes and uremia are conditions with increased proneness toward impaired EDD and hemostasis abnormalities that could accelerate atherosclerosis (13,15–18).

Pancreas transplantation could slow the progression of atherosclerosis and could improve endothelial function in uremic type 1 diabetic patients (13).

Recent studies have shown that exogenous C-peptide can improve neural and vascular function in diabetic rats and can restore nitric oxide (NO) synthase expression, which is impaired in diabetic patients (19–23). Islet transplantation is an appealing alternative to pancreas transplantation, given that with classic

Table 1—Pretransplant characteristics in type 1 diabetic kidney-transplanted patients with successful islet transplantation (SI-K) or unsuccessful islet transplantation (UI-K)

	SI-K group	UI-K group	P
n	21	13	
Age (years)	41.2 ± 1.3	40.6 ± 3.8	NS
Sex (M/F)	11/10	11/2	0.04
C-peptide levels	0.14 ± 0.02	0.15 ± 0.03	NS
Duration of diabetes (years)	26.5 ± 2.1	26.7 ± 1.7	NS
Glycated hemoglobin (%)	8.1 ± 0.2	7.7 ± 0.6	NS
Body weight (kg)	59.7 ± 2.0	59.3 ± 3.1	NS

Data are mean ± SEM. No differences were observed between the two groups except for sex distribution.

immunosuppression a persistent C-peptide secretion could be obtained for a long period of time. Our aim was to evaluate whether islet transplantation could affect survival, cardiovascular death rate, and endothelial function in kidney-transplanted type 1 diabetic patients.

RESEARCH DESIGN AND METHODS

Patients

A total of 34 type 1 diabetic kidney-transplanted patients underwent islet transplantation and were followed for an average of 53.4 ± 7.09 months until 1 January 2001 or until they were lost to follow-up due to exitus or other causes. The general characteristics of the patients before transplantation are summarized in Table 1. All the patients were C-peptide negative (<0.5 ng/ml) before transplantation (Table 1). C-peptide levels reported at each time of follow-up were assessed during hospitalization. Exclusion criteria for transplantation were as follows: 1) previous strokes, 2) major amputations, 3) severe dilated cardiomyopathy, and 4) coronary artery disease. Before transplantation none of the patients had a pathological ejection fraction or heart failure. Furthermore, all of the patients who entered the islet transplantation program at our institute were carefully evaluated for known cardiovascular risk factors. No differences were evident with regards to electrocardiogram, perfusional myocardial scintigraphy, echocardiography, and carotid and lower limb arterial status, as evaluated by Doppler ultrasonography.

Patients were divided into two groups according to the presence or absence of C-peptide secretion: the successful islet-kidney-transplanted (SI-K) group (fasting C-peptide serum concentration >0.5

ng/ml for >1 year, 21 patients, mean follow-up 46 ± 9 months) and the unsuccessful islet-kidney-transplanted group (UI-K) (fasting C-peptide serum concentration <0.5 ng/ml, 13 patients, mean follow-up 63 ± 13 months).

All of the patients were evaluated for cumulative survival, cardiovascular death rate, C-peptide secretion, insulin requirement, and metabolic control. Subgroups of patients underwent the following investigations aimed at studying the vascular function: 1) 24 patients (16 SI-K, 8 UI-K) were studied for EDD, NO levels, atherothrombotic risk factors such as vWF and DDF levels cross-sectionally; 2) 19 patients (13 SI-K, 6 UI-K) were studied for intima-media thickness (IMT) progression; and 3) 12 patients (6 SI-K, 6 UI-K) underwent skin biopsy for pathological examination, cross-sectionally. Patients were pooled together to perform correlations between C-peptide-to-creatinine ratio/HbA_{1c} and parameters under investigations. An informed consent was obtained for every study.

Islet isolation and transplantation

Patients underwent kidney transplantation according to ABO match. Eight patients received simultaneous Langherans islet transplantation, while the others received islet transplantation after kidney transplantation. Islets were isolated from pancreas obtained from multiorgan donors, according to a modification of the automated method and purified by centrifugation on a discontinuous gradient previously described (4,24). Islets were then cultured in a humidified atmosphere (5% CO₂) in M199 medium supplemented with 10% FCS, 100 units/ml penicillin, 100 µg/ml streptomycin sulfate, and 2 mmol/l glutamine (Seromed Biochrom, Berlin, Germany). Preparations

were considered adequate for transplantation according to the following criteria: 1) sterility (aerobic, anaerobic, fungal, and mycoplasma assessment); 2) number of equivalent islets >6,000/kg body wt; 3) purity >20% (morphometric determination of islet/total mass); and 4) islet viability. Transplantation was performed between 12 and 48 h after isolation. Percutaneous transhepatic injection (under local anesthesia) was performed according to the protocol approved by the Institutional Review Board. All patients were already under immunosuppression therapy with steroids and cyclosporine for a previous kidney transplant. After induction with ATG (125 mg/day for 10 days) (Thymoglobulin; Merieux, Lyon, France) immunosuppression was based on cyclosporine (7.5 mg · kg⁻¹ · day⁻¹), mycophenolate mofetil (2 g/day), and methylprednisone (10 mg/day). Steroids were withdrawn within 3–6 months after islet transplantation.

Patient survival and cardiovascular events

Patients actuarial survivals were calculated. Cardiovascular death rate was assessed according to ICD-9.

IMT

Patients underwent ultrasonographic analysis of IMT of the carotid artery (11) 3.1 ± 0.5 years after islet transplantation. The examinations were repeated 3 years later and the variation of the IMT was calculated. Ultrasonographic analysis of the carotid artery was done with a high-resolution ultrasound scanner (Acuson 128 Xp/10) equipped with a linear array 3.5- to 5-MHz transducer. Optimal axial resolution is ~0.20 mm. The analysis limited to the “far wall” of a restricted area of common carotid artery was at least 1 cm below the bifurcation; the start of the carotid bifurcation was evaluated as the point of loss of parallel configuration of the far and near wall. IMT was defined as the distance from the leading edge of the lumen-intima interface and the leading edge of the media-adventitia interface of the far wall. The mean of the right and the left longitudinal common carotid artery IMT measurements was used in the analysis. Intraobserver variability varied between a mean ± SD difference of 0.02 ± 0.02 mm in selected and trained group (13), which is quite similar to our reproducibility.

Skin biopsy

Patients underwent skin-punch biopsy on the internal surface of the arm 4.5 ± 1.2 years after transplantation (25). Microvessel lesions were evaluated on routinely stained paraffin-embedded sections. Two different rabbit polyclonal antibodies directed against the vWF (Dako, Copenhagen, Denmark and Biomedica, Hayward, CA), and a polyclonal antibody directed against endothelial constitutive NO synthase (ecNOs) (Santa Cruz Biotechnology, Santa Cruz, CA) were used. The immunoreactivity was independently scored by two different pathologists (S.L. and S.U.) on at least 10 capillaries. Anti-vWF and anti-vimentin antibodies (Dako) were used for immunoelectron microscopy experiments (26). A score of endothelial cell injury was calculated at ultra-structural examination, each feature (rough endoplasmic reticulum, cisternae dilation, microvilli ramification, vimentin-like filament, chromatin condensation, and irregular nuclear contour) was evaluated based on a scale from 0 (normal) to 3 (highly pathological).

Endothelial function, NO production, and atherothrombotic risk factors

Patients underwent EDD, NO, and atherothrombotic risk factor assessment 4.2 ± 0.9 years after transplantation. EDD, circulating levels of vWF, DDF, and NO levels were determined as previously described (13,27,28). Patients were then pooled together and the parameters of endothelial function were correlated with C-peptide and HbA_{1c}. EDD was assessed by evaluation of flow increase after hyperemia. Endothelial-independent dilation was studied by vasodilation mediated by nitrates. Anteroposterior diameter was evaluated as parameters of endothelial function. Diameter of the artery was preferentially evaluated in B-mode. An occluding forearm cuff placed 5 cm below the antecubital fossa was inflated to 50 mmHg above systolic pressure for 5 min and then released to induce reactive local hyperemia. Recordings were made 5, 60, and 120 s after onset of reactive hyperemia and 3 min after sublingual administration of nitroglycerine spray (400 mg). In each case, the arm without shunt was used for the test. Our reproducibility for EDD performed in control groups ranged from 2.5 to 3.0% (13).

Laboratory assessment

Fasting levels of cyclosporine, creatinine, HbA_{1c}, serum C-peptide, total cholesterol, and triglycerides were assayed yearly (13). Due to a potential confounding effect of C-peptide renal clearance, C-peptide is reported as C-peptide-to-creatinine ratio. vWF was determined by an immunoelectrophoresis method based on the use of polyclonal goat IgG anti-human vWF (American Diagnostic, Greenwich, CT) (13). Serum C-peptide levels (intra-assay CV 3.0%; interassay CV 3.0%) were assayed by radioimmunoassay using commercial kits (Medical System, Genova, Italy). NO levels were assayed by measurement of the end products of their metabolism [i.e., nitrite and nitrate levels (NO₂-/NO₃-)], using enzymatic catalysis coupled with Griess reaction. Specifically, NO₃- was reduced to NO₂- by 0.1 unit nitrate reductase, 5×10^{-6} mol/l flavinadenine dinucleotide, and 250×10^{-6} mol/l nicotinamide adenine dinucleotidephosphate (reduced form). Samples were incubated at 37°C for 3 h, 8.8 units lactate dehydrogenase and 10^{-2} mol/l pyruvate were added to each well, and the sample was incubated for 90 min at 37°C. Finally, Griess reactives were added to each well, and the sample was read at 540 nm. The other parameters were assessed with common laboratory kit assay.

Statistical analyses

All the data were expressed as mean \pm SEM. The cumulative survival was evaluated with a Wilcoxon test. A multivariate analysis (Cox analysis) was used to determine the effect of sex on survival. Differences between parameters were evaluated using Student's *t* test when parameters were normally distributed, Mann-Whitney *U* test when parameters were not normally distributed, and a χ^2 test for categorical variables. Correlations were assessed with a Spearman rank correlation coefficient.

RESULTS

General characteristics

Before transplantation, the two groups were similar for the most important characteristics (Table 1). No differences for creatinine levels, fasting serum insulin, lipid profile, arterial blood pressure, cyclosporine levels, kidney rejection rate, and smoking habits (data not shown)

were observed during the follow-up. A statistical difference was evident for systolic blood pressure (SBP) at baseline (SI-K 135.6 ± 8.8 vs. UI-K 148.2 ± 6.2 mmHg, $P = 0.04$). However, this difference was no longer observed at 2 (SI-K 140.2 ± 5.4 vs. UI-K 149.0 ± 6.3 mmHg, NS) and 4 years (SI-K 143.3 ± 8.8 vs. UI-K 150.0 ± 6.2 mmHg, NS). Sex distribution appeared significantly different in the two groups (Table 1). As shown, the UI-K group has a longer follow-up than the SI-K group, although not statistically significant. The accrual rate in the two groups during the whole follow-up was similar except in 1991 (SI-K 0 vs. UI-K 3, $P = 0.048$) and in 2000 (SI-K 7 vs. UI-K 0, $P = 0.02$). At the moment of cross-sectional studies, no differences were evident for creatinine (SI-K 1.3 ± 0.1 vs. UI-K 1.5 ± 0.2 mg/dl), SBP (SI-K 143.3 ± 8.8 vs. UI-K 148.8 ± 5.6 mmHg), diastolic blood pressure (DBP) (SI-K 83.3 ± 3.6 vs. UI-K 84.4 ± 2.4 mmHg), and lipid profile (data not shown). Immunosuppression and medical treatment during the follow-up were similar in the two groups.

Patient survival and cardiovascular death rate

The SI-K group showed a statistically significant ($P = 0.04$) higher patient survival than the UI-K group at 10 years (Fig. 1A). A statistical difference was evident in sex distribution between the SI-K and the UI-K group (Table 1). However, analyzing our data in a multivariate analysis (Cox analysis), inserting sex as a cofactor, does not appear to have a significant impact on survival ($P = 0.89$, relative risk 1.12 [95% CI 0.21–5.8]). Cardiovascular death rate (according to ICD-9) was higher in the UI-K group than in the SI-K group (SI-K 1/21 vs. UI-K 4/13, $\chi^2 = 3.9$, $P = 0.04$).

Glycometabolic control

C-peptide secretion was higher in the SI-K group than in the UI-K group (Fig. 1B), insulin requirement was lower in the SI-K group than in the UI-K group (Fig. 1C), and no statistical difference in HbA_{1c} levels was observed in the two groups (Fig. 1D).

IMT

A stabilization of IMT was observed in the SI-K group ($\Delta 1-3$ years -13 ± 30 μ m),

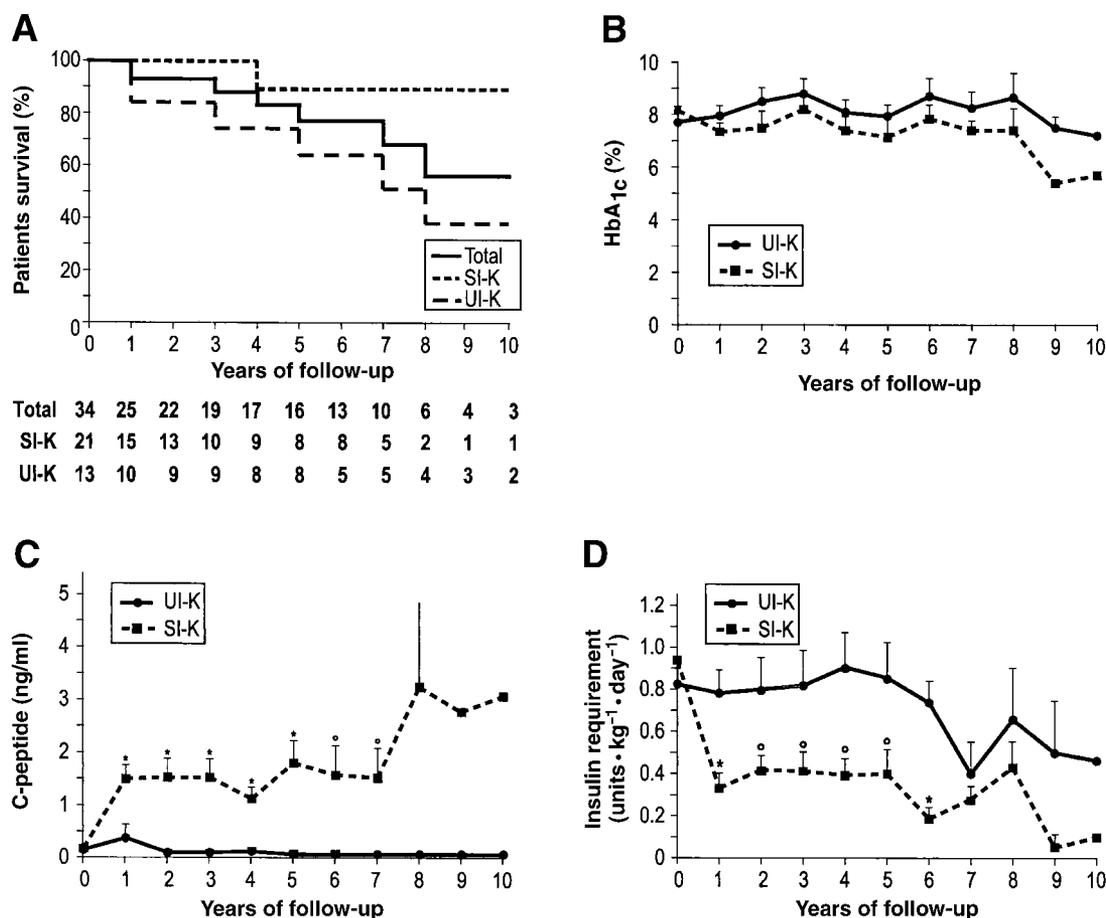


Figure 1—Patients cumulative survival (Wilcoxon test, $P = 0.04$) (A), and mean HbA_{1c} (B), C-peptide levels (C), and exogenous insulin requirement (D) in type 1 diabetic kidney-transplanted patients with successful islet transplantation (SI-K) or failed islet transplantation (UI-K). (* $P < 0.01$, $^{\circ}P < 0.05$).

while IMT increased in the UI-K group ($\Delta 1-3$ years $245 \pm 20 \mu m$) ($P = 0.03$).

Skin biopsy

Histopathology and immunohistochemistry. Morphologic evaluation of routinely stained sections from skin biopsy specimens did not show any specific skin disease apart from lesions of diabetic microangiopathy. In particular, periodic acid Schiff stains demonstrated an increase of basal membrane thickness of dermal capillaries in both SI-K and UI-K groups, with no significant differences between them. vWF and eNOS immunohistochemical expression in endothelial cells was higher in the SI-K than in the UI-K group (Fig. 2).

Electron microscopy. The basal membrane thickness was slightly lower in the SI-K group than in the UI-K group (SI-K $1,488 \pm 276$ vs. UI-K $1,628 \pm 790$ nm, NS). The endothelial cells of cutaneous

capillaries of the SI-K group showed lower cell injury compared with capillaries of the UI-K group. The endothelial cells of the UI-K group showed microvillar blebbing, dilated endoplasmic reticulum (Fig. 3A and B), condensation of vimentin filaments (Fig. 3C and D), and irregular nuclear contour with chromatin condensation more prominent than those of the SI-K group (Fig. 3E and F). A global score of microvascular/endothelium injury was significantly better in the SI-K group than in the UI-K group (Table 2).

Endothelial function, NO production, and atherothrombotic risk factors

The SI-K group showed a higher EDD than the UI-K group (EDD [SI-K] $7.8 \pm 4.5\%$ vs. [UI-K] $0.5 \pm 2.7\%$, $P = 0.02$), higher basal NO level (SI-K 42.9 ± 6.5 vs. UI-K $20.2 \pm 6.8 \mu mol/l$, $P = 0.02$), and lower levels of vWF (SI-K 138.6 ± 15.3

vs. UI-K $180.6 \pm 7.0\%$, $P = 0.02$) and DDF (SI-K 0.61 ± 0.22 vs. UI-K $3.07 \pm 0.68 \mu g/ml$, $P < 0.01$). EDD and NO serum levels positively correlated with C-peptide-to-creatinine ratio ($r = 0.43$, $P = 0.04$ and $r = 0.50$, $P = 0.01$, respectively) while vWF and DDF serum levels negatively correlated with C-peptide-to-creatinine ratio ($r = -0.51$, $P = 0.01$ and $r = 0.74$, $P < 0.01$, respectively). None of these parameters correlated with HbA_{1c} .

The SI-K group was subdivided according to higher or lower levels of C-peptide (divided on the basis of 50 percentiles) (higher 1.30 ± 0.16 vs. lower 3.27 ± 0.62 ng/ml, $P < 0.01$). Patients with higher levels of C-peptide showed normal EDD (higher 12.8 ± 4.0 vs. lower $4.1 \pm 4.3\%$, NS), higher NO levels (higher 42.5 ± 7.3 vs. lower $29.4 \pm 7.9 \mu mol/l$, NS), and reduced vWF (higher 111.6 ± 16.8 vs. lower $164.8 \pm 22.9\%$, NS) and DDF (higher 0.46 ± 0.13 vs. lower $1.15 \pm$

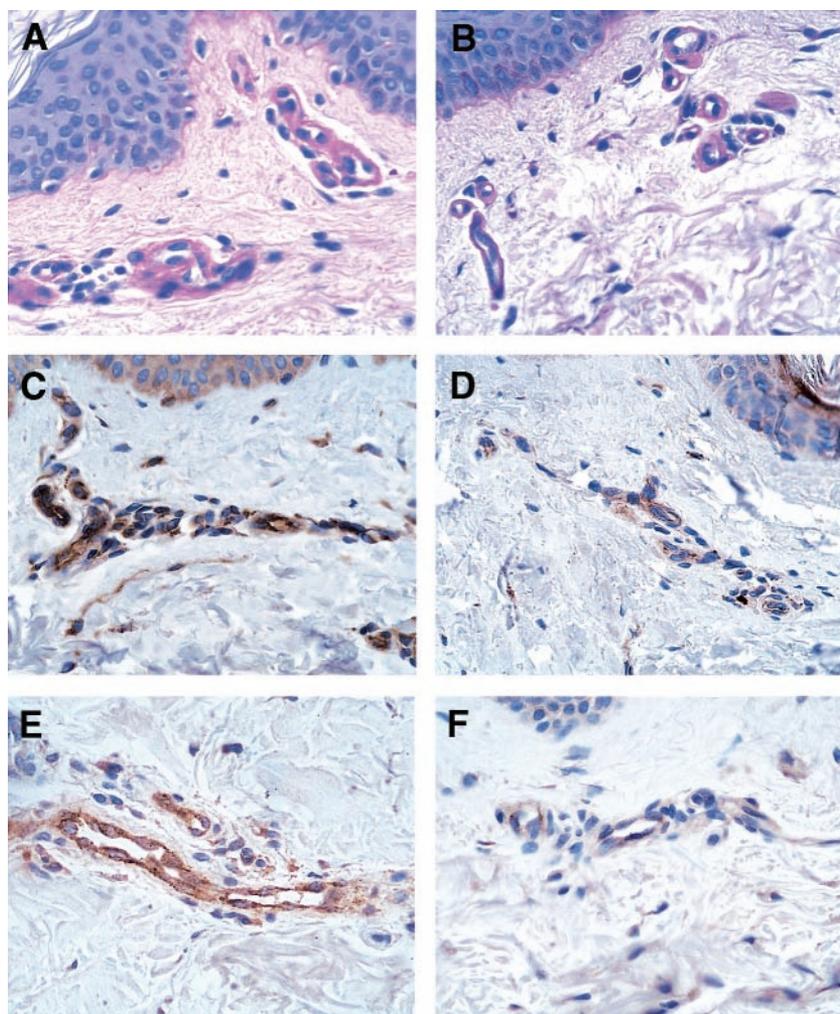


Figure 2—Immunohistochemical analysis of skin biopsies performed in type 1 diabetic kidney-transplanted patients with successful islet transplantation (SI-K, no. 34) or failed islet transplantation (UI-K, no. 3) (original magnification 200 \times). A: Periodic acid Schiff in an SI-K patient. B: Periodic acid Schiff in a UI-K patient. C: vWF vascular expression in an SI-K patient. D: vWF vascular expression in a UI-K patient. E: ecNOs vascular expression in an SI-K patient. F: ecNOs vascular expression in a UI-K patient.

0.80 $\mu\text{g/ml}$, NS) levels, when compared with patients with lower C-peptide levels.

CONCLUSIONS— Survival in uremic type 1 diabetic patients undergoing hemodialysis is extremely poor (12,29). Kidney-pancreas transplantation doubles life expectancy in these patients (12,29). In this report we describe, for the first time, the long-term beneficial effects of islet transplantation on survival and micro- and macrovascular complications in 34 type 1 diabetic kidney-transplanted patients at a single institution.

Survival in patients with functioning islets is similar to kidney-pancreas-transplanted patients, and is better than in patients with nonfunctioning transplanted islets (12,29). Because of sex mismatch, the results of our analysis on patients' survival in the UI-K and SI-K groups have been reanalyzed in a multivariate analysis. Sex does not appear to be a confounding factor for survival.

IMT is an important index for eventual cardiovascular disease. For each 100 μm of IMT, the risk of acute myocardial infarction increased by 11% (13). The worsening of IMT in the UI-K group is higher than the value observed in the general population (30 $\mu\text{m}/3$ years), but is similar to the population with ischemic heart disease (90–200 $\mu\text{m}/3$ years) (30). Islet function could play a role in preventing atherosclerosis and impairment of microvascular reactivity characteristics of diabetes and related conditions (31). Although no pretransplant analysis has been performed for the variable that we have studied in these patients, it is unlikely that the data observed could be attributed to differences at baseline. The two groups were studied in detail and were similar for major known cardiovascular risk factors and status.

Endothelial function positively correlates with C-peptide-to-creatinine ratio but does not correlate with HbA_{1c} levels.

Endothelial function reflects the ability of the endothelium to produce NO, which is impaired in uremia and in long-term hyperglycemia (22,32–34). As reported in the rat model, restoration of C-peptide secretion may protect endothelial function via ecNOs activation (19). vWF and DDF are well-established markers of endothelial dysfunction and incipient atherosclerosis (13). The higher levels of these two soluble markers in the patients with lower C-peptide levels suggest proneness toward accelerated atherosclerosis.

Histology and immunohistochemistry of skin biopsies did not show major morphological differences, although a reduced expression of vWF and ecNOs was evident in the vessels of the UI-K group. The alterations most frequently reported in electron microscopy include thickening of the capillary basement membrane (35), cell swelling, dilated endoplasmic reticulum in endothelial cells, and separations of interendothelial junctions

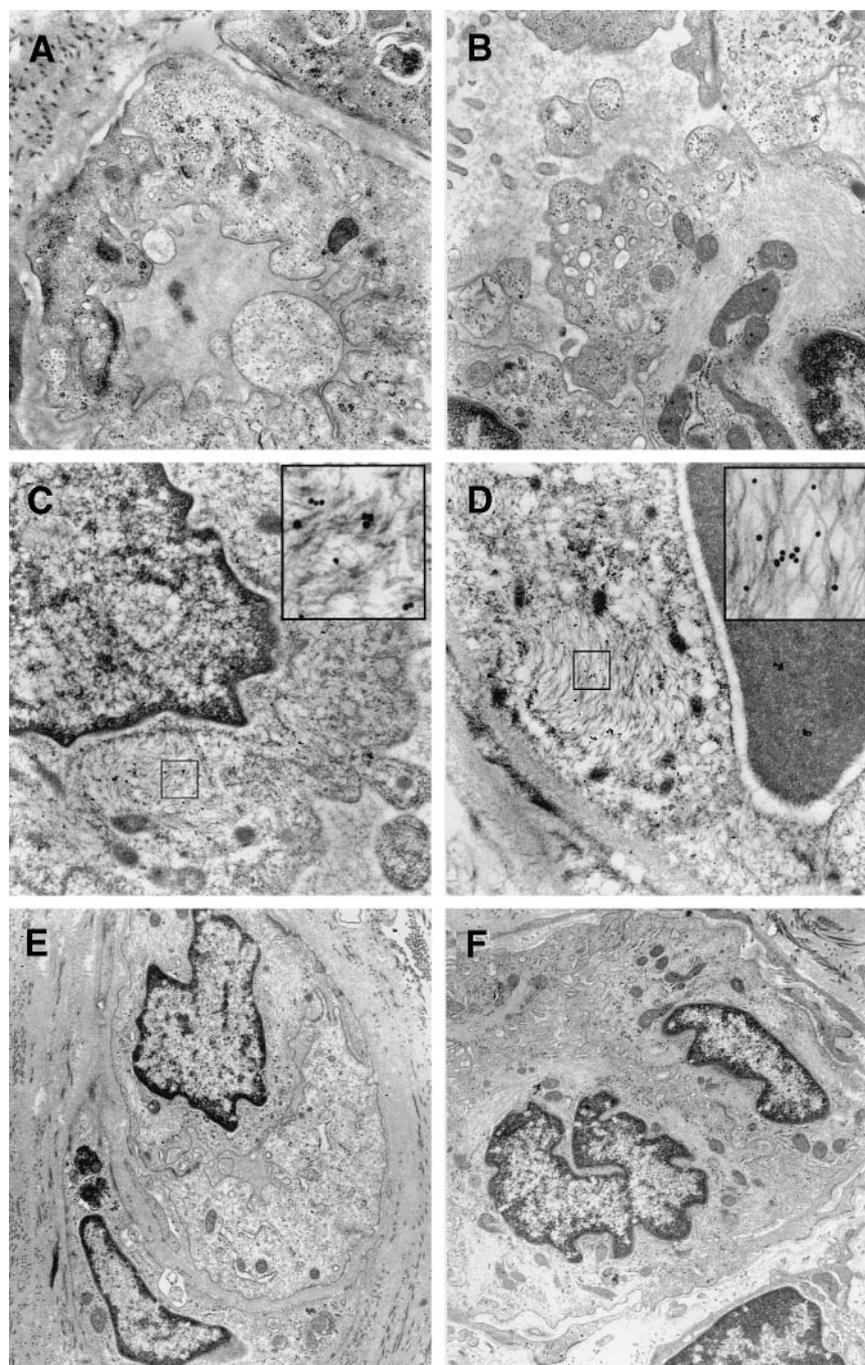


Figure 3—Electron microscopy analysis in type 1 diabetic kidney-transplanted patients with successful islet transplantation (SI-K) or failed islet transplantation (UI-K). A: Microvilli ramification and cisternae dilation in a SI-K patient (no. 13) (final magnification 13,000 \times). B: Microvilli ramification and cisternae dilation in a UI-K patient, (no. 21) (final magnification 13,000 \times). C: Vimentin-like filament in an SI-K patient (no. 13) (final magnification 13,000 \times); inset: anti-vimentin immunogold labeling (final magnification 22,000 \times). D: Vimentin-like filament in a UI-K patient (no. 21) (final magnification 13,000 \times); inset: anti-vimentin immunogold labeling (final magnification 22,000 \times). E: Nuclear aspect and chromatin pattern in an SI-K patient (no. 24) (final magnification 6,300 \times). F: Nuclear aspect and chromatin pattern in a UI-K patient (no. 21) (final magnification 6,300 \times).

(35,36). Basal membranes were thicker in the UI-K group than the SI-K group, perhaps because of the continuous process of

endothelial cell death and regeneration (35,37,38). Furthermore, accumulation of bundles of vimentin filaments could be

considered a sign of degeneration or a consequence of hemodynamic modifications (39). Our frequent observation of nuclear irregular shapes, most frequent in the UI-K group, can be explained either as an aspect of endothelial damage (40) or as a consequence of rearrangement in the vimentin filaments. In fact, in many cells, intermediate filaments are closely associated with the nucleus, suggesting a function in nuclear anchoring or signaling (41). The presence of nuclear chromatin condensation indicating apoptosis in endothelial cells in the UI-K group is consistent with previous studies showing a role of hyperglycemia in the induction of apoptosis in islet and endothelial cells (26,41).

The beneficial effects of functioning islets could be the consequence of an improved metabolic control and of the restoration of islet endocrine function in the SI-K group. Interestingly, during the follow-up, the SI-K reached values of HbA_{1c} similar to those found by Diabetes Control and Complications Trial to prevent diabetic microvascular complications (9). The subanalysis in the SI-K group suggests that there are some beneficial effects of restoring islet endocrine function, after splitting the patients into two groups according to higher or lower C-peptide levels. However, at this time it is difficult to distinguish between effects mediated by 1) improvement of glycometabolic control, 2) restoration of islet endocrine function, and 3) some undetectable differences that might have been present between the two groups, making the SI-K group healthier than the UI-K group.

Pancreas transplantation and, to a lesser extent, islet transplantation reduce insulin resistance in type 1 diabetic patients (42,43), which is a major risk factor for cardiovascular disease (44). Islet graft restoration of endogenous C-peptide secretion may also play a beneficial effect through the modulation of ecNOs. It is also possible that C-peptide replacement may prevent the development or retard the progression of chronic complications in type 1 diabetes by a variety of mechanisms, including augmented blood flow in skeletal muscle and skin, diminished glomerular hyperfiltration, and improved nerve function (45).

In conclusion, this study shows that successful islet transplantation improves the overall survival, cardiovascular out-

Table 2—Scoring of electron microscopy characteristics (indicating endothelial cell suffering), obtained from skin biopsies of type 1 diabetic kidney-transplanted patients with SI-K or UI-K

	SI-K	UI-K	P
Cisternae dilation	2.5 (1.0–3.0)	3.0 (2.7–3.0)	NS
Microvilli ramification	2.0 (1.0–3.0)	2.0 (2.0–3.0)	NS
Vimentin-like filament	2.0 (1.7–3.0)	3.0 (2.0–3.0)	NS
Chromatin condensation	1.0 (1.0–2.0)	2.5 (2.0–3.0)	0.01
Irregular nucleus	0.5 (0.5–1.0)	1.0 (1.0–1.0)	0.01
Global score	8.2 (6.7–10.6)	11.0 (10.7–12.2)	0.01

Data are median (interquartile range). A clear apoptotic pattern of endothelial cells is evident in the UI-K group.

comes, and endothelial function in type 1 diabetic kidney-transplanted patients. We hypothesize that islet transplantation could exert its beneficial effects, by not only improving blood glucose control, but also by partial restoration of endocrine islet function.

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