Islet Transplantation Is Associated with Improvement of Renal Function among Uremic Patients with Type I Diabetes Mellitus and Kidney Transplants

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Abstract. The potential effects of islet transplantation on the renal function of 36 patients with type I diabetes mellitus and kidney transplants were studied with 4 yr of follow-up monitoring. Kidney-islet recipients were divided into two groups, i.e., patients with successful islet transplants (SI-K group) (n = 24, fasting C-peptide levels of >0.5 ng/ml for >1 yr) and patients with unsuccessful islet transplants (UI-K group) (n = 12, fasting C-peptide levels of <0.5 ng/ml). Kidney graft survival rates and function, urinary albumin excretion rates, and sodium handling were compared. Na⁺/K⁺-ATPase activity in protocol kidney biopsies and in red blood cells was cross-sectionally analyzed. The SI-K group demonstrated better kidney graft survival rates (100, 83, and 83% at 1, 4, and 7 yr, respectively) than did the UI-K group (83, 72, and 51% at 1, 4, and 7 yr, respectively; P = 0.02). The SI-K group demonstrated reductions in exogenous insulin requirements and higher C-peptide levels, compared with the UI-K group, whereas GFR values were similar. Microalbuminuria (urinary albumin index) increased significantly in the UI-K group only (UI-K, from 92.0 ± 64.9 to 183.8 ± 83.8, P = 0.05; SI-K, from 108.5 ± 53.6 to 85.0 ± 39.0, NS). In the SI-K group, but not in the UI-K group, natriuresis decreased at 2 and 4 yr (P < 0.01). The SI-K group demonstrated greater Na⁺/K⁺-ATPase immunoreactivity in renal tubular cells (P = 0.05) and higher activity in red blood cells (P = 0.03), compared with the UI-K group. The Na⁺/K⁺-ATPase activity in red blood cells was positively correlated with circulating C-peptide levels but not with glycated hemoglobin levels. Successful islet transplantation was associated with improvements in kidney graft survival rates and function among uremic patients with type I diabetes mellitus and kidney grafts.

Diabetes mellitus is a chronic metabolic disorder that affects various organs, including nerves, heart, and kidneys (1). A variety of structural and metabolic defects are involved in the progression of chronic diabetic complications, and enzymatic disorders of the plasma membrane have been reported (1). Na⁺/K⁺-ATPase, the activity of which is required for specific functions of different tissues, has been demonstrated to be impaired among diabetic patients (2,3). Na⁺/K⁺-ATPase activity in the kidney can influence natriuresis, because >50% of sodium handling is mediated by Na⁺/K⁺-ATPase (3). Recent reports demonstrated that insulin could regulate the activity of Na⁺/K⁺-ATPase (2,4).

Islet transplantation is a safe procedure, especially after kidney transplantation, and could be an alternative to pancreas transplantation for the restoration of endogenous insulin secretion among patients with type I diabetes mellitus (5–10). Successful islet grafting leads to improvements in glucose, protein, and lipid metabolism and diabetic microangiopathy and macroangiopathy (5–7,11,12). Endogenous insulin and C-peptide secretion is restored for years for approximately two-thirds of recipients, with complete insulin independence for a minority of patients (5–11). It was recently demonstrated that C-peptide is a bioactive peptide that acts through the stimulation of endothelial constitutive nitric oxide synthase and Na⁺/K⁺-ATPase of renal tubular cells (13,14). Our aim was to evaluate whether islet transplantation was associated with improvements in kidney graft survival rates and function among patients with type I diabetes mellitus and kidney grafts.

Materials and Methods

Patients and Study Design

Thirty-six C-peptide-negative patients with type I diabetes mellitus and kidney transplants underwent islet transplantation. All patients demonstrated panel reactive antibody levels of <10% and negative cross-matching results. Before transplantation, none of the patients exhibited an abnormal myocardial ejection fraction or heart failure. After islet transplantation, the recipients were divided into two groups, according to the outcome of the islet grafting, i.e., successful islet transplantation after kidney transplantation (SI-K group) (fasting serum C-peptide levels of >0.5 ng/ml for >1 yr, n = 24) or unsuccessful islet transplantation after kidney transplantation (UI-K group)
...informed consent was obtained for all studies. In the weight of the recipient, (aerobic, anaerobic, fungal, and mycoplasmal assessments), 2 mM glutamine (Seromed Biochrom, Berlin, Germany), for 12 to 20.4 mo; UI-K, 115.9 ± 20.4 mo; NS) and islet (SI-K, 65.2 ± 8.3 mo; UI-K, 80.5 ± 14.1 mo; NS) transplant follow-up periods were comparable for the two groups. Subgroups of patients underwent the following additional investigations: (1) 22 patients (SI-K, 14 patients; UI-K, eight patients) underwent assessments of Na⁺/K⁺-ATPase activity in red blood cells; (2) 16 patients (SI-K, eight patients; UI-K, eight patients) underwent assessments of urinary albumin excretion and natriuresis; and (3) 10 patients (SI-K, five patients; UI-K, five patients) underwent assessments of Na⁺/K⁺-ATPase expression in protocol kidney biopsies. Informed consent was obtained for all studies.

Islet Isolation and Transplantation

Patients underwent islet transplantation according to ABO matching. Islets were isolated from pancreases obtained from multiorgan donors with a modification of the automated method and were then purified by centrifugation on discontinuous Ficoll gradients, as described previously (8). Islets were then cultured in a humidified atmosphere (5% CO₂), in M199 medium supplemented with 10% fetal bovine serum, preshaken (200 rpm) 3 times at 37°C with a 1 mM potassium phosphate buffer (pH 7.4), with or without 0.1 mM ouabain. The ionophore was removed by washing of the cells four times at 37°C with a 1 mM potassium phosphate buffer (pH 7.4) containing 50 mM choline chloride, 50 mM KCl, and 50 mM NaCl, centrifuged, and resuspended for 10 min in the same solution without ouabain. The islets were then washed three times at 37°C with a 1 mM potassium phosphate buffer (pH 7.4) containing 50 mM sucrose, 50 mM choline chloride, 50 mM KCl, and 50 mM NaCl, 10 mM glucose, and 1 mg/ml bovine serum albumin. Na⁺-loaded cells were washed four times with the aforementioned washing solution. After centrifugation, Na⁺-loaded erythrocytes were resuspended in ice-cold washing buffer. Aliquots of erythrocytes were transferred into efflux medium, yielding hematocrit values of 3 to 4% for each efflux incubate. Na⁺ and Na⁺-ouabain efflux media contained 75 mM MgCl₂, 85 mM sucrose, and 5 mM KCl in 10 mM Tris-MOPS buffer (pH 7.4 at 37°C), with or without 0.1 mM ouabain. Two aliquots of each incubate were obtained at the beginning of the incubation (at 37°C) and after 15 and 30 min, chilled in melting ice, and centrifuged at 4°C. Supernatants were used for measurement of Na⁺ concentrations by atomic absorption spectrophotometry (Perkin Elmer model 4000, Boston, MA). Na⁺ efflux rates in each medium were calculated as the changes in Na⁺ concentrations with time, in a simple linear regression analysis, and were expressed as millimoles of Na⁺ per cell per hour. Na⁺ pump activity was taken as the difference between Na⁺ efflux rates in Na⁺ and Na⁺-ouabain media.

Renal Biopsies

Patients underwent protocol biopsies of the transplanted kidney 2.0 ± 0.8 yr after islet transplantation. All biopsy specimens were evaluated by a pathologist in a blinded manner and were scored according to the Banff 97 classification (18). Expression of the α1 subunit of Na⁺/K⁺-ATPase in renal tubular cells was detected in immunocytochemical analyses. After antigen retrieval with microwave treatment in sodium citrate buffer, sections were incubated with a monoclonal antibody against the α1 subunit of Na⁺/K⁺-ATPase (Upstate Bio-
technology, Lake Placid, NY) and a secondary antibody conjugated with fluorescein (19).

**Statistical Analyses**

Data are expressed as means ± SEM. Differences between parameters were evaluated with the *t* test when parameters were normally distributed and with the Mann-Whitney *U* test when parameters were not normally distributed. Correlations were assessed with a Spearman rank correlation coefficient. For graft survival analyses, patient deaths were counted as graft losses, regardless of the functional status of the graft at the time of death (20). The Wilcoxon rank-sum test was used to compare the two groups. Variables that could influence graft failure were included in a multivariate Cox regression analysis. All reported *P* values were two-tailed.

**Results**

**General Characteristics**

Before islet transplantation, the two groups of patients were similar with respect to most of the tested parameters. In particular, no differences were evident with respect to age (SI-K, 41.9 ± 1.2 yr; UI-K, 40.6 ± 2.6 yr; NS), duration of diabetes mellitus (SI-K, 27.2 ± 1.9 yr; UI-K, 26.7 ± 1.7 yr; NS), C-peptide levels (SI-K, 0.15 ± 0.02 ng/ml; UI-K, 0.16 ± 0.04 ng/ml; NS), HbA1c levels (SI-K, 8.1 ± 0.2%; UI-K, 7.2 ± 0.4%; NS), body weight (SI-K, 59.0 ± 1.9 kg; UI-K, 59.3 ± 3.2 kg; NS), number of transplanted islets (Table 1), and kidney cold ischemia time (SI-K, 14.6 ± 1.44 h; UI-K, 11.3 ± 0.8 h; NS). Four patients in the UI-K group and 12 patients in the SI-K group (NS) received multiple islet infusions (mean number of infusions, UI-K, 1.3 ± 0.1; SI-K, 1.7 ± 0.2; NS). The two groups of recipients exhibited similar patterns of rejection episodes, cytomegalovirus infections, and kidney retransplantation (Table 1). The mean numbers of HLA matches for the kidney and panel reactive antibody levels were similar for the two groups (Table 1). The mean numbers of HLA matches for the pancreas were statistically significantly different between the two groups (Table 1). Immunosuppressive therapy, lipid profiles, and medications were similar for the two groups. In particular, cyclosporine levels were as follows: 242.9 ± 39.2, 205.1 ± 42.2, and 130.5 ± 18.22 ng/ml for the UI-K group and 256.0 ± 34.5, 164.3 ± 12.7, and 184.1 ± 21.0 ng/ml for the SI-K group at follow-up times of 0, 2, and 4 yr, respectively (NS). Angiotensin-converting enzyme inhibitors were used for three patients in the SI-K group and two patients in the UI-K groups (NS). After steroid withdrawal, no kidney or islet rejections were evident. At 6 mo after islet transplantation, when almost all of the patients had completed steroid withdrawal, a significant reduction in HbA1c levels (basal, 7.8 ± 0.2%; 6 mo, 7.2 ± 0.2%; *P* = 0.01) for the entire group of patients was evident. This reduction was associated with GFR stability (basal, 56.3 ± 3.7 ml/min; 6 mo, 58.8 ± 3.6 ml/min; NS) and with a nonsignificant decrease in creatinine levels (basal, 1.71 ± 0.22 mg/dl; 6 mo, 1.43 ± 0.09 mg/dl; NS).

**Islet Graft Survival Rates and Function**

In the SI-K group, 23 patients exhibited evidence of islet graft function at 1 yr after transplantation, 21 patients at 2 yr, and 12 patients at 4 yr. C-peptide levels were higher in the SI-K group than in the UI-K group (Figure 1A), whereas insulin requirements were lower in the SI-K group than in the UI-K group (Figure 1B). In particular, significant reductions in insulin requirements in the SI-K group were evident (−60.9 ± 7.9, −49.1 ± 9.5, and −54.8 ± 9.5% at 1, 2, and 4 yr after transplantation, respectively; all *P* < 0.05), whereas the insulin requirements in the UI-K group remained stable (−0.1 ± 14.0, −8.5 ± 16.2, and −2.0 ± 10.4% at 1, 2, and 4 yr after transplantation, respectively; NS). No significant differences in HbA1c levels were observed between the two groups during the follow-up period (Figure 1C). Twelve patients maintained insulin inde-

![Figure 1](https://example.com/figure1.png)

**Figure 1.** C-peptide levels (A), exogenous insulin requirements (EIR) (B), and mean glycated hemoglobin (HbA1c) levels (C) among patients with type 1 diabetes mellitus and kidney transplants with successful islet transplants (SI-K group) or unsuccessful islet transplants (UI-K group). C-peptide levels were higher and exogenous insulin requirements were lower in the SI-K group, whereas HbA1c levels were similar in the two groups (*P* < 0.01, °*P* < 0.05).
pendence for >3 mo (full-function group). The mean duration of insulin independence in that group was 21.5 ± 4.2 mo.

Kidney Graft Survival Rates and Function

The SI-K group demonstrated better kidney graft survival rates (100, 83, and 83% at 1, 4, and 7 yr, respectively) than did the UI-K group (83, 72, and 51% at 1, 4, and 7 yr, respectively) ($P = 0.02$). Cox regression analysis demonstrated no correlations between kidney graft survival rates and the duration of type I diabetes mellitus ($df = 1, P = 0.6$), body weight ($df = 1, P = 0.3$), pretransplant age ($df = 1, P = 0.3$), and basal creatinine levels ($df = 1, P = 0.1$). No differences in GFR or creatinine levels between the SI-K and UI-K groups were evident during the follow-up period (Figure 2, A and B). A progressive reduction of glycosuria at 2 and 4 yr was evident among patients in the SI-K and UI-K groups. GFR and creatinine levels were similar in the two groups, whereas a worsening of urinary albumin excretion was evident in the UI-K group.

Table 1. Immunologic and general characteristics of patients with type I diabetes mellitus and kidney transplants who underwent successful islet transplantation (SI-K group) or unsuccessful islet transplantation (UI-K group)$^a$

<table>
<thead>
<tr>
<th></th>
<th>SI-K ($n = 24$)</th>
<th>UI-K ($n = 12$)</th>
<th>$P$ Value</th>
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</thead>
<tbody>
<tr>
<td>No. of transplanted islets/kg</td>
<td>11,056 ± 1,424</td>
<td>8,140 ± 1,635</td>
<td>NS</td>
</tr>
<tr>
<td>Mean no. of rejection episodes before islet transplantation</td>
<td>0.2 ± 0.1</td>
<td>0.5 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Mean no. of CMV infection episodes</td>
<td>0.33 ± 0.11</td>
<td>0.50 ± 0.19</td>
<td>NS</td>
</tr>
<tr>
<td>No. of patients with CMV infections</td>
<td>7</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>No. of kidney retransplants</td>
<td>1</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>No. of HLA matches for kidney</td>
<td>2.21 ± 0.21</td>
<td>2.14 ± 0.55</td>
<td>NS</td>
</tr>
<tr>
<td>No. of HLA matches for pancreas</td>
<td>1.38 ± 0.24</td>
<td>0.79 ± 0.18</td>
<td>0.05</td>
</tr>
</tbody>
</table>

$^a$ No differences in the numbers of rejection cytomegalovirus (CMV) infection episodes, or retransplants were evident. No differences in the numbers of HLA matches for the kidney were evident. In contrast, a slight difference in the numbers of HLA matches for the transplanted pancreas was evident.

Figure 2. GFR calculated with the Cockcroft-Gault equation (A), creatinine levels (B), urinary albumin excretion/urinary creatinine concentration ratios (UI-K at 4 yr versus basal, $P = 0.05$) (C), and relative changes in the urinary sodium excretion rate (UNaV) (SI-K at 4 yr versus basal, $P < 0.01$; SI-K versus UI-K at 4 yr, $*P = 0.03$) (D) among patients in the SI-K and UI-K groups. GFR and creatinine levels were similar in the two groups, whereas a worsening of urinary albumin excretion was evident in the UI-K group.

Figure 3. Systolic BP (SBP) (A), diastolic BP (DBP) (B), aldosterone levels (C), and renin levels (D) among patients in the SI-K and UI-K groups. Systolic BP was lower in the SI-K group at the 4-yr follow-up time ($*P = 0.01$).
only in the SI-K group (basal: SI-K, 4.7 ± 1.7 g/24 h; UI-K, 4.5 ± 1.6 g/24 h; NS; 2 yr: SI-K, 0.7 ± 0.5 g/24 h; UI-K, 5.3 ± 2.0 g/24 h; \( P < 0.01 \); 4 yr: SI-K, 1.9 ± 1.5 g/24 h; UI-K, 6.9 ± 2.2 g/24 h; \( P = 0.02 \); SI-K at 2 yr versus basal, \( P = 0.04 \)).

Urinary Albumin Excretion

An increase in the urinary albumin index was observed for the UI-K group, whereas the index remained stable in the SI-K group (Figure 2C). Two patients (one in the UI-K group and one in the SI-K group) were markedly macroalbuminuric; even for those patients, however, trends similar to those for the respective groups were evident, with a reduction for the patient in the SI-K group (from 471.0 to 331.0) and an increase for the patient in the UI-K group (from 481.0 to 633.0) 4 yr after islet transplantation. One patient in the SI-K group and six in the UI-K group demonstrated increases in urinary albumin excretion (\( P = 0.04 \)). A negative correlation between the changes in urinary albumin excretion and C-peptide/creatinine ratios was evident (\( r = -0.56, P = 0.02 \)), whereas no correlation with HbA1c levels was observed.

Natriuresis

In the SI-K group, a progressive reduction in natriuresis at 2 and 4 yr was evident. In the SI-K group, UNaV decreased (Figure 2D), whereas FeNa remained stable (basal, 1.38 ± 0.27%; 4 yr, 1.29 ± 0.19%; NS). In the UI-K group, UNaV remained stable (Figure 2D) and FeNa increased, although not statistically significantly (basal, 1.47 ± 0.35%; 4 yr, 1.82 ± 0.57%; NS).

Arterial BP and the Renin-Angiotensin System

A statistically significant difference in systolic BP was evident at the 4-yr follow-up time, with lower values in the SI-K group (\( P = 0.01 \)) (Figure 3A). A slight nonsignificant difference in diastolic BP between the two groups was evident at baseline (Figure 3B). The mean dosages of furosemide were similar for the two groups of patients (SI-K, 12.5 ± 8.5 mg/d; UI-K, 18.6 ± 8.3 mg/d; NS) during the entire follow-up period, with similar levels of diuresis. Renin and aldosterone levels were similar for the two groups during the entire follow-up period (Figure 3, C and D).

\( Na^{+}/K^{+} \)-ATPase Activity in Kidney Biopsies

No major differences were evident in the kidney biopsies for the two groups. In particular, no differences in Banff 97 scores could be detected. All biopsies were morphologically classified as normal. However, we could observe the following features. Four patients in the SI-K group and two in the UI-K group exhibited mild tubular injury (Table 2). One patient in each group exhibited a scanty cellular infiltrate, whereas one patient in the UI-K group exhibited glomerular basement membrane thickening (Table 2). None of the patients in the UI-K group demonstrated detectable Na\(^+/K^{+}\)-ATPase immunoreactivity in renal tubular cells, whereas four patients in the SI-K group clearly demonstrated expression of Na\(^+/K^{+}\)-ATPase (\( P = 0.05 \)) (Figure 4, A, C, and D).

\( Na^{+}/K^{+} \)-ATPase Activity in Red Blood Cells

Na\(^+/K^{+}\)-ATPase activity was statistically significantly higher in the red blood cells of patients in the SI-K group, compared with those in the UI-K group (Figure 4B). Furthermore, Na\(^+/K^{+}\)-ATPase activity was positively correlated with C-peptide/creatinine ratios (\( r = 0.44, P = 0.04 \)) but not with HbA1c levels.

Subanalysis of the SI-K Group

In our analysis of the SI-K group, we separately analyzed data for patients who maintained insulin independence for >3 mo (full-function group, 12 patients) and patients who did not (partial-function group, 12 patients), comparing both groups with the UI-K group. There were no differences in kidney graft survival rates (UI-K, 83, 72, and 51%; partial-function, 100, 84, and 84%; full-function, 100, 82 and 82% at 1, 4, and 7 yr, respectively) or GFR (basal versus 4 yr: UI-K, +9.6 ± 13.6 ml/min; partial-function, +8.9 ± 8.5 ml/min; full-function, +6.2 ± 11.1 ml/min) between the partial-function and full-function groups. All other parameters demonstrated a trend toward improvement in the full-function group, compared with the partial-function group. In particular, a higher Na\(^+/K^{+}\)-ATPase activity in red blood cells (UI-K, 2.99 ± 0.24 mmol of Na\(^+/\)L cell per h; partial-function, 3.18 ± 0.34 mmol of Na\(^+/\)cell per h; full-function, 4.20 ± 0.34 mmol of Na\(^+/\)cell

Figure 4. Scores of Na\(^+/K^{+}\)-ATPase α1 subunit expression in the kidney (A) and Na\(^+/K^{+}\)-ATPase activity in the red blood cells (B) of patients in the SI-K and UI-K groups and Na\(^+/K^{+}\)-ATPase α1 subunit expression in the kidneys of patients in the SI-K group (patient 34) (C) or the UI-K group (patient 12) (D). Na\(^+/K^{+}\)-ATPase activity was statistically significantly higher in the red blood cells (\( *P = 0.03 \)) and in the kidney (\( ^{c}P = 0.05 \)) of patients in the SI-K group, compared with those in the UI-K group. The patients in the UI-K group did not exhibit detectable Na\(^+/K^{+}\)-ATPase immunoreactivity in renal tubular cells, whereas the patients in the SI-K group clearly demonstrated expression of Na\(^+/K^{+}\)-ATPase.
Interestingly, whereas studies of patients with kidney-pancreas or kidney-only transplants could be biased by the different baseline conditions at enrollment, this was not true for our SI-K and UI-K groups, because both groups contained patients with kidney-only transplants. Furthermore, in a comparison of the kidney graft survival rate of the kidney-islet transplant group with the graft survival rate of our kidney-diabetes mellitus group, islet transplantation was associated with an improvement in kidney graft survival rates. Even in a comparison of the entire group of kidney-islet transplant patients with our populations of uremic patients with type I diabetes mellitus and kidney transplants, a better kidney survival rate was evident in the kidney-islet transplant group, compared with the kidney-diabetes mellitus groups (at 4 yr: kidney-islet, 80%; kidney-diabetes mellitus, 42%; chi-square = 10.2, P < 0.01).

Other immunosuppressive protocols were recently proposed for islet transplantation. However, their safety among patients with kidney transplants has not been validated.

It is possible that a tendency toward a more active immunologic status could be present, even in a latent manner, in the UI-K group. It is possible that patients with better renal graft function also experienced some improvement in islet graft function. However, no evidence of more rejection episodes or cytomegalovirus infections, higher panel reactive antibody levels, more kidney retransplants, or more HLA matches for the kidney could be detected. A slight but statistically significant difference in islet HLA matching between the two groups could be detected, suggesting a possible explanation for different islet graft outcomes. However, islet failure is probably related not only to immunologic factors but also to other factors; previous studies suggested that one-half of transplanted islets are lost because of ischemia and subsequent apoptosis and that B cells are particularly sensitive to injury, compared with A cells (21,22). Furthermore, hyperglycemia could precipitate islet apoptosis, causing the failure of the remaining islets.

It has been demonstrated that the alterations in Na+/K+-ATPase activity induced by diabetes mellitus develop similarly in the kidney and in red blood cells and that the average erythrocyte Na+/K+-ATPase activity is reduced among diabetic patients (2,4,23). Intensive insulin treatment can partially increase Na+/K+-ATPase activity and sensitivity to sodium,

<table>
<thead>
<tr>
<th>Histologic Features</th>
<th>SI-K</th>
<th>UI-K</th>
</tr>
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<tbody>
<tr>
<td>Kidney biopsy Banff 97 score</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tubules</td>
<td>4 patients exhibited mild tubular injury; 1 patient exhibited tubular atrophy with slight interstitial fibrosis</td>
<td>2 patients exhibited mild tubular injury; 1 patient exhibited tubular atrophy with slight interstitial fibrosis</td>
</tr>
<tr>
<td>Infiltrate</td>
<td>1 patient exhibited slight signs of lymphogranulocytic infiltrates</td>
<td>1 patient exhibited slight signs of lymphogranulocytic infiltrates</td>
</tr>
<tr>
<td>Glomeruli</td>
<td>Normal</td>
<td>1 patient exhibited thickening of the glomerular basement membrane</td>
</tr>
</tbody>
</table>

*All biopsies were classified as normal.*

Discussion

The long-term effects of islet transplantation on kidney graft survival rates and function among patients with type I diabetes mellitus and kidney grafts have not been previously evaluated. We demonstrated that islet transplantation, probably by partially restoring pancreatic endocrine function, not only improves the metabolic control of diabetes mellitus but also is associated with improvements in renal function and kidney graft life span. In particular, islet transplantation decreases the urinary excretion of albumin, reduces FeNa, and reduces UNaV. These clinical events are associated with increases in Na+/K+-ATPase activity in red blood cells and increased expression of Na+/K+-ATPase immunoreactivity in tubular cells of the transplanted kidney. The detection of increased expression of Na+/K+-ATPase in the renal biopsy specimens from patients in the SI-K group might explain the increased renal handling of sodium observed for those patients after islet transplantation. A significant correlation between the Na+/K+-ATPase activity in red blood cells and the C-peptide/creatinine ratio, but not HbA1c levels, was detected among those patients. Furthermore, a beneficial effect on systolic BP was evident. Finally, no major differences in renal biopsy morphologic features between the two groups could be detected. These findings were reinforced by the evidence that, when the SI-K group was divided into partial-function and full-function (insulin-independent) subgroups, improvements in almost all studied parameters were evident in the full-function group.

Islet transplantation improves microvascular and macrovascular function and patient survival rates, whereas pancreas transplantation confers adjunctive benefits in kidney graft survival rates among uremic patients with type I diabetes mellitus (11,12,20). Interestingly, whereas studies of patients with kidney-
thus decreasing the excretion of sodium (24–26). The activation of Na+/K+-ATPase plays a major role in the increased reabsorption of salt and osmotically obliged water (27). Indeed, >50% of the active net reabsorption of sodium chloride in Henle’s loop is attributable to Na+/K+-ATPase activity (28). It is interesting to note that patients with kidney transplants demonstrate particular clinical features. The function of the denervated kidney is characterized by significant increases in UNaV and FeNa, with a concomitant reduction in Na+ content (24–26). The activation of Na+/K+-ATPase activity (28). Moreover, immunosuppressive drugs (i.e., steroids) increase the activity of Na+/K+-ATPase in renal tissue, thus increasing net tubular sodium reabsorption (29).

The differences in natriuresis observed for the two groups of patients cannot be explained on the basis of GFR deterioration, because creatinine levels remained similar in the two groups. The observation of improved excretion of sodium in the SI-K group is intriguing and supports the hypothesis that impaired sodium excretion may play a role in the development of experimental nephropathy (30). Increased sodium excretion is detected in the early stage of diabetic nephropathy, when glomerular hyperfiltration is associated with microalbuminuria. Intensive insulin treatment can partially correct this abnormality (31,32). In this setting, activation of the renin-angiotensin system might enhance “pressure natriuresis” and increase natriuresis (33). The possibility of different degrees of activation of the renin-angiotensin-aldosterone system in the two groups can reasonably be excluded, as indicated by renin and aldosterone levels. Moreover, reduced sodium handling can increase the solute load at the tubular level and induce glomerular feedback, which influences the renin-angiotensin system (33).

The reduction of glycosuria in the SI-K group is of interest; because glucose and sodium are filtered together, it is possible that improvements in glycosuria may influence natriuresis. However, the improvement in metabolic control induced by islet transplantation does not seem to be responsible for the observed beneficial effects on the function of the transplanted kidney, because HbA1c levels were similar in the two groups during the entire follow-up period.

Patients with functioning islet grafts exhibited a stabilization of urinary albumin excretion, which, conversely, worsened in the UI-K group. Because microalbuminuria is a sensitive marker of progressive renal failure, this evidence supports the conclusion that good islet graft function could be associated with the improvement of transplanted kidney function (16). Such beneficial effects may also depend on the restoration of endogenous C-peptide secretion of the transplanted islets. The C-peptide receptor was recently cloned (13,14), which strongly suggests that C-peptide might have biologic activity. Indeed, C-peptide has been demonstrated to induce glomerular vasodilation and could slow the progression of diabetic nephropathy in the transplanted kidney (34). It has also been demonstrated that C-peptide may stimulate endothelial constitutive nitric oxide synthase and modulate the activity of Na+/K+-ATPase. Endogenous C-peptide levels differed significantly in the two groups of patients, being absent in the SI-K group (Figure 1). Therefore, although long-term exogenous insulin independence is not always achieved after islet transplantation, restoration of C-peptide secretion may represent a valid indication for performing islet transplantation among patients with kidney grafts. A possible confounding effect on urinary albumin excretion could be related to the improvement of systolic BP observed in the SI-K group. Because the two groups were treated similarly with respect to hypertension, this could suggest beneficial effects of islet transplantation on the cardiovascular system, as recently reported (11), and on BP.

We hypothesize that, in the SI-K group, restoration of endogenous C-peptide secretion may activate Na+/K+-ATPase in renal tubular cells, thus inducing an increase in sodium handling and reductions in FeNa and UNaV. Such activation can protect the kidney from the excessive sodium loading resulting from renal denervation, impaired Na+/K+-ATPase activity, and treatment with steroids (34,35). In addition, C-peptide-induced glomerular vasodilation might decrease pressure natriuresis and increase nitric oxide availability, thus increasing the handling of sodium and reducing the urinary albumin excretion rate (36). Of note, this seems to be confirmed by the relatively smaller, but statistically significant, increase in systolic BP in the SI-K group during the follow-up period. Long-term insulin independence is the final goal of islet transplantation. In fact, we observed a trend toward improvement of renal function in the subset of the SI-K group that achieved insulin independence. The positive effects of normalization of glycometabolic control with pancreas transplantation on transplanted and native kidney function were previously demonstrated (20,31).

In conclusion, successful islet transplantation is associated with improvement of kidney graft survival rates, restoration of Na+/K+-ATPase activity, reduction of natriuresis, and improvement of urinary albumin excretion among patients with type I diabetes mellitus and kidney grafts. We hypothesize that islet transplantation exerts its beneficial effects by restoring endogenous C-peptide secretion, insulin secretion, and glycometabolic control.

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References


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