The Beneficial Effects of Pancreas Transplant Alone on Diabetic Nephropathy

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**OBJECTIVE** — Pancreas transplant alone can be effective in significantly improving the quality of life of type 1 diabetic patients, and it can also eliminate acute diabetes complications, such as hypoglycemic and/or hyperglycemic episodes. The effects of pancreas transplant alone on long-term complications of diabetes, including nephropathy, are still not settled. We evaluated whether restoration of long-lasting normoglycemia by pancreas transplant alone might have beneficial action on diabetic nephropathy.

**RESEARCH DESIGN AND METHODS** — A total of 32 type 1 diabetic patients were evaluated before and 1 year after successful pancreas transplant alone, together with 30 matched nontransplanted type 1 diabetic subjects. Several metabolic and kidney function parameters were measured, including plasma glucose, glycohemoglobin (A1C), C-peptide, plasma lipids, blood pressure, creatinine, creatinine clearance, and urinary protein excretion.

**RESULTS** — Pancreas transplant alone restored sustained normoglycemia, without exogenous insulin administration, and improved plasma lipid levels. Blood pressure decreased significantly. Creatinine concentrations and clearances did not differ before and after transplantation. Urinary protein excretion decreased significantly after pancreas transplant alone, with four microalbuminuric and three macroalbuminuric patients who became normoalbuminuric. None of these changes occurred in the nontransplanted group.

**CONCLUSIONS** — Successful pancreas transplant alone, through restoration of sustained normoglycemia, improves diabetic nephropathy in type 1 diabetic patients.

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Diabetic nephropathy is the most common single cause of end-stage renal disease in the U.S. and Europe (1). In the U.S., this late diabetes complication accounts for ~40% of new cases of end-stage renal disease, with costs that exceed $15 billion per year (1). Epidemiological data show that ~20–30% of patients with diabetes develop nephropathy (1–4). The earliest clinical sign of nephropathy is the appearance of low but abnormal levels (>30 mg/day or 20 μg/min) of albumin in the urine, referred to as microalbuminuria. Without specific interventions, 80% of subjects with type 1 diabetes who develop sustained microalbuminuria have their urinary albumin excretion increase at a rate of 10–20% per year to the stage of overt nephropathy or clinical albuminuria (up to 300 mg/24 h or 200 μg/min) over a period of 10–15 years, with hypertension also developing along the way. Once overt nephropathy occurs, without specific treatment the glomerular filtration rate gradually falls over a period of several years at a rate that is highly variable from individual to individual (2–20 ml · min⁻¹ · year⁻¹). Eventually, end-stage renal disease develops in 50% of type 1 diabetic individuals with overt nephropathy within 10 years and in >75% by 20 years. In addition to its being the earliest manifestation of nephropathy, proteinuria is a marker of greatly increased cardiovascular morbidity and mortality for patients with diabetes (5,6). A recent study evaluated a group of patients with type 1 diabetes of at least 30 years with baseline and 5 years of follow-up (7). Death occurred in 26 and 44% of patients with micro- or macroalbuminuria at baseline, respectively.

Hyperglycemia represents the necessary precondition for the development and progression of diabetic nephropathy, and indeed it has been clearly demonstrated that tight glycemic control can substantially delay the onset and progression of this complication (8,9). Furthermore, aggressive antihypertensive treatment as well as the use of renin-angiotensin system inhibitors can reduce and in some cases abolish microalbuminuria in type 1 diabetic patients (10). Interestingly, in eight patients with type 1 diabetes, Fioretto et al. (11) demonstrated that pancreas transplantation could reverse the structural lesions of diabetic nephropathy after 10 years of insulin independence. However, in these patients proteinuria did not change significantly and creatinine clearance decreased significantly after grafting (values before transplantation and at 1 year posttransplantation of 108 ± 20 and 65 ± 12 ml · min⁻¹ · 1.73 m⁻², respectively). Therefore, the issue of whether the solitary pancreas transplantation procedure has a favorable impact on the native kidneys is still unclear. We studied 32 patients with type 1 diabetes who received a successful solitary pancreas transplantation. These patients were evalu-
RESEARCH DESIGN AND METHODS — Altogether, 62 type 1 diabetic patients were enrolled into the study, which was performed with the approval of the ethics committee of the University of Pisa. As shown in Table 1, there was no major difference at baseline between the control and the transplanted groups with regard to the main clinical characteristics. The number of patients on antihypertensive or antidyslipidemic agents was also similar in the two groups (Table 1). In particular, 10 patients (33%) in the nontransplanted group and 17 patients (53%) in the group of patients who then received pancreas transplant alone were on ACE inhibitors. Indications for solitary pancreas transplantation (12–14) were the presence of two or more overt diabetes complications (23 patients, 72%) and/or glucose hyperlability with hypoglycemic unawareness and impaired quality of life (9 patients, 28%). The number of patients in the nontransplanted group with these two conditions were 21 (70%) and 9 (30%), respectively. Major contraindications included age >60 years, active smoking, obesity (BMI >30 kg/m²), left ventricular ejection fraction <40%, active malignancy or infection, and unstable psychological profile. Pancreas donors had the following characteristics: age 33 years (range 17–49), 21 male and 11 female donors, HLA matching of 2.5 (range 2–4), intensive care unit stay 79 h (range 22–216), and cold ischemia time <12 h.

Procedures. Grafting into recipients was performed through a midline intraperitoneal approach (15). All the grafts were transplanted according to the technique of portal-enteric drainage (16). Briefly, the portal vein of the pancreas was anastomosed end-to-side to a major tributary of the superior mesenteric vein, whereas the donor iliac artery bifurcation graft was anastomosed end-to-side to the right common iliac artery. The transplanted duodenum was then anastomosed side-to-side to a diverting Roux-en-Y limb of recipient jejunum. For prevention of rejection, induction therapy consisted of 20 mg basiliximab on the day of transplant and 4 days later, and maintenance therapy was based on tacrolimus (given at doses to achieve blood through levels of 10–15 ng/ml during the first month posttransplant and 8–12 ng/ml thereafter), mycophenolate mophetil (1–2 g per day) and steroids (500 mg on the day of transplant, followed by tapering to 5 mg per day after 3 months).

The following parameters were assessed before transplantation and at 1 year after grafting (where not otherwise defined, all the parameters were assessed by common laboratory kit assay): body weight, blood pressure (measured three times with a sphygmomanometer after sitting position for at least 10 min; the mean of the last two measurements was recorded), fasting plasma glucose, glycohemoglobin (A1C), fasting C-peptide, fasting total cholesterol and triglycerides, HDL cholesterol, LDL cholesterol (by the Friedewald equation), serum creatinine, creatinine clearance (by the Cockcroft-Gault formula (17), and urinary protein excretion (1).

Statistical analysis. Data are presented as the means ± SD. Statistical analysis was performed by the Wilcoxon test for comparison of data at baseline and at 1 year of follow-up within the control or transplanted group and by the Mann-Whitney U test for comparison of data between control and transplanted groups.

RESULTS — In the control group, no metabolic parameter changed significantly at the 1 year observation in comparison with baseline values (Table 2). Conversely, in the transplanted patients, all of the measured variables (with the exception of HDL cholesterol and triglycerides) improved significantly 1 year after transplantation.

### Table 1—Main clinical characteristics of patients included in the study, at baseline

<table>
<thead>
<tr>
<th></th>
<th>Nontransplanted group</th>
<th>Transplanted group</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>30</td>
<td>32</td>
</tr>
<tr>
<td>Age (years)</td>
<td>39 ± 10</td>
<td>37 ± 9</td>
</tr>
<tr>
<td>Male/female subjects</td>
<td>17/13</td>
<td>16/16</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>22 ± 11</td>
<td>24 ± 10</td>
</tr>
<tr>
<td>Insulin dose (IU/day)</td>
<td>39 ± 8</td>
<td>46 ± 10</td>
</tr>
<tr>
<td>Number of patients on antihypertensive therapy</td>
<td>12*</td>
<td>18†</td>
</tr>
<tr>
<td>Number of patients on statin therapy</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

Data are means ± SD, unless otherwise indicated. *10 patients on ACE inhibitors; †17 patients on ACE inhibitors.

### Table 2—Some metabolic data of nontransplanted and transplanted patients at baseline and after 1 year

<table>
<thead>
<tr>
<th></th>
<th>Fasting plasma glucose (mg/dl)</th>
<th>A1C (%)</th>
<th>C-peptide (ng/ml)</th>
<th>Total cholesterol (mg/dl)</th>
<th>LDL cholesterol (mg/dl)</th>
<th>HDL cholesterol (mg/dl)</th>
<th>Triglycerides (mg/dl)</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>212 ± 89</td>
<td>8.4 ± 1.5</td>
<td>0.02 ± 0.00</td>
<td>220 ± 36</td>
<td>140 ± 29</td>
<td>61 ± 17</td>
<td>126 ± 79</td>
<td>23.8 ± 3.0</td>
</tr>
<tr>
<td>1 year</td>
<td>188 ± 88</td>
<td>8.0 ± 1.3</td>
<td>0.02 ± 0.00</td>
<td>206 ± 42</td>
<td>128 ± 32</td>
<td>63 ± 18</td>
<td>128 ± 101</td>
<td>23.9 ± 3.3</td>
</tr>
<tr>
<td>Transplanted</td>
<td>250 ± 105</td>
<td>9.0 ± 2.0</td>
<td>0.01 ± 0.00</td>
<td>210 ± 36</td>
<td>134 ± 35</td>
<td>61 ± 16</td>
<td>111 ± 56</td>
<td>23.5 ± 3.02</td>
</tr>
<tr>
<td>1 year</td>
<td>85 ± 10*</td>
<td>5.3 ± 0.4*</td>
<td>2.7 ± 1.1*</td>
<td>190 ± 37†</td>
<td>117 ± 28†</td>
<td>59 ± 17</td>
<td>120 ± 61</td>
<td>23.3 ± 2.9</td>
</tr>
</tbody>
</table>

Data are means ± SD. *P < 0.01 vs. transplanted, baseline, and nontransplanted; †P < 0.05 vs. transplanted, baseline.
Pancreas transplant and diabetic nephropathy

Figure 1—Blood pressure values in nontransplanted, control (ctrl), and pancreas transplant alone (tx) type 1 diabetic patients at baseline and after 1 year. *P < 0.02 vs. baseline. diast, diastolic; syst, systolic.

Pancreas transplantation (Table 2). At the 1 year control, four patients in the nontransplanted group and three patients in the transplanted group were on statin therapy. Blood pressure values did not differ at baseline between nontransplanted patients (136 ± 28 and 77 ± 9 mmHg for systolic and diastolic, respectively) and transplanted patients (130 ± 13 and 80 ± 10 mmHg) (Fig. 1). However, in the transplanted patients, at 1 year after transplantation, blood pressure values were significantly lower than at baseline (121 ± 11 and 75 ± 8 mmHg) (Fig. 1). Notably, seven pancreas transplant recipients stopped their antihypertensive treatment, so that the number of transplanted patients on ACE inhibitors at 1 year posttransplant were 10 (vs. 17 pretransplant).

Creatinine and creatinine clearance at baseline were, respectively, 1.00 ± 0.40 mg/dl and 84.4 ± 28 ml/min in control subjects and 0.95 ± 0.25 mg/dl and 95.4 ± 30 ml/min in patients waiting for pancreas transplantation (both NS vs. control group). After 1 year, no significant change had occurred in the control group (creatinine 1.02 ± 0.41 mg/dl, creatinine clearance 82.0 ± 29.0 ml/min) or in the transplanted group (1.00 ± 0.19 mg/dl, 88.0 ± 28.9 ml/min).

The amount of urinary protein at baseline was similar in the control group (1.45 ± 2.45 g/24 h) compared with successively transplanted patients (1.20 ± 2.44 g/24 h). After 1 year of follow-up, the protein excretion amount did not change in control patients (1.40 ± 1.90 g/24 h, NS vs. baseline), and it decreased significantly in transplanted patients (0.67 ± 1.58 g/24 h, P < 0.05 vs. baseline).

At baseline, 9 of the control patients were normoalbuminuric, 14 were microalbuminuric, and 7 were macroproteinuric. In these subgroups, during the follow-up all of the normoalbuminuric patients became microalbuminuric, whereas no change occurred in the patients in the other grades of proteinuria. The results obtained in the transplanted group are further detailed in Fig. 2A–F. Before transplantation, 8 patients were normoalbuminuric, 10 were microalbuminuric, and 14 were macroalbuminuric (Fig. 2A, C, and E). In these subgroups, at 1 year after pancreas transplant alone, all of the normoalbuminuric subjects remained as such, four patients of the microalbuminuric subgroup became normoalbuminuric, and three patients with low-grade macroalbuminuria became normoalbuminuric (Fig. 2A, C, and E). No apparent change of creatinine clearance was observed after transplantation in these subgroups (Fig. 2B, D, and F). In the seven patients who returned to normoalbuminuria, pre- and posttransplant body weight (60.9 ± 11.5 vs. 60.0 ± 8.8 kg), creatinine levels (0.95 ± 0.15 vs. 0.95 ± 0.14 mg/dl), and use of ACE inhibitors (five versus four patients) were superimposable.

**CONCLUSIONS**—This study demonstrates for the first time that in type 1 diabetic patients, successful pancreas transplant alone determines improvement of diabetic nephropathy, as documented by a significant reduction of average urinary excretion rate and regression of proteinuria in several patients 1 year after transplantation. These effects were accompanied by no statistically significant change of creatinine concentration or clearance. The beneficial actions of pancreas transplant alone are unlikely to be attributable to anatomical changes in the native kidneys. In fact, it has been previously demonstrated that reversal of diabetic kidney lesions occurred many years after pancreas grafting (11). Intriguingly, in that study, proteinuria did not change significantly, and creatinine clearance worsened markedly (~40% at 1 year after transplantation) (11). Other factors that we exclude as having contributed to the observed effects are the use of ACE inhibitors, other antihypertensive medications, and/or the use of statins. Actually, in the present study, patients used less antihypertensive medication after transplantation than before the pancreas graft. This rules out the possibility that the reduced proteinuria could be attributable to inhibition of the renin-angiotensin system (10,18).

Instead, we believe that restoration of endogenous insulin and C-peptide secretion, with the consequent normalisation of blood glucose levels and improvement of other metabolic parameters, do, directly or indirectly, play the fundamental role. Improvement of glucose levels has been associated with reduced hyperfiltration and diminished albumin excretion rate (19), and it is well known that reducing blood glucose levels in type 1 diabetic patients at diagnosis determines disappearance of microalbuminuria, which sometimes may be detected at diabetes onset (20). In addition, hyperglycemia can acutely increase membrane permeability to macromolecules (21). Finally, hyperglycemia can raise blood pressure by inducing renal sodium retention and extravascular shift of fluid and sodium (22). Normalization of glucose values as achieved and maintained in our patients by pancreas transplant alone may therefore contribute to reduction of blood pressure (as indeed we have found) and, as a consequence, prevent the deleterious effects of blood pressure on glomerular filtration (23).

It was recently reported that regression of microalbuminuria in type 1 diabetic patients was associated with lower lipid levels (24). Interestingly, in our pancreas-transplanted patients, not only did glucose levels normalize, but, in addition,
total and LDL cholesterol concentrations decreased, which could have contributed to the beneficial effects of pancreas transplant alone on the kidney. Obviously, further studies are needed to confirm these findings and to investigate the mechanisms possibly involved.

By successful pancreas transplantation, the endogenous secretion of insulin and C-peptide was restored. It has long been recognized (25) that insulin may cause reduction of urinary albumin excretion rate by renal vasoconstriction. This phenomenon is usually accompanied by increased blood pressure (26). This mechanism seems unlike the one(s) in our group of patients because blood pressure decreased significantly after transplantation. Rather, we are inclined to believe that C-peptide endogenously produced by the pancreas graft might play a role. In fact, C-peptide can bind to cell membranes, including endothelial cells, and stimulate nitric oxide synthase, thus...
Pancreas transplant and diabetic nephropathy

contributing to vascular homeostasis (27). C-peptide administration in streptozotocin-induced diabetic animals resulted in normalization of diabetes-induced glomerular hyperfiltration, reduction of urinary albumin excretion, and diminished glomerular expansion (28). The former two effects have also been observed in type 1 diabetic patients given C-peptide in replacement doses for up to 3 months (29).

Remarkably, the use of immunosuppression as administered in the present study did not damage kidney function, at least for the duration of the 1-year follow-up. In particular, we used a calcineurin inhibitor, tacrolimus, which may cause renal impairment by inducing vasoconstriction (30). However, current use of calcineurin inhibitors, including tacrolimus and cyclosporine, is safer than a few years ago because of the reduction of doses and optimization of plasma levels (31,32).

In conclusion, the present study demonstrates, for the first time, that successful pancreas transplantation alone in type 1 diabetic patients improves diabetic nephropathy, as shown by reduced proteinuria and unchanged creatinine levels and clearance at 1 year after transplantation. Of course, these novel findings need to be confirmed in studies with longer follow-up. Nevertheless, the demonstration of the beneficial effects of pancreas transplantation alone in the native kidneys of diabetic patients supports the concept of considering pancreas transplantation alone as an useful therapeutic option in type 1 diabetic patients.

References