Pancreas Transplantation Improves Vascular Disease in Patients With Type 1 Diabetes

Jennifer L. Larsen, MD
Christopher W. Colling, BS
Tanapon Ratanasuwann, MD
Tab W. Burkman, BS
Thomas G. Lynch, MD
Judi M. Erickson, RN, CDE
Elizabeth R. Lyden, MS
James T. Lane, MD
Lynn R. Mack-Shipman, MD

OBJECTIVE — Pancreas transplantation (PTX) normalizes glucose and improves microvascular complications, but its impact on macrovascular disease is still debated.

RESEARCH DESIGN AND METHODS — Carotid intima-media thickness (IMT), shown to correlate with cardiovascular disease (CVD) risk and events, was determined prospectively by ultrasonography in successful pancreas transplant recipients to evaluate the effect of PTX on CVD risk. Carotid IMT and CVD risk factors of pancreas transplant recipients (n = 25) were compared with three groups: individuals with type 1 diabetes without significant nephropathy (n = 20), nondiabetic kidney transplant recipients (n = 16), and normal control subjects (n = 32). Mean age of pancreas transplant recipients at the time of transplantation was 42.4 ± 1.2 years (mean ± SE) and duration of diabetes was 25.9 ± 1.4 years.

RESULTS — After PTX, HbA1c level (P < 0.0001) decreased to normal and, whereas creatinine level (P = 0.0002) decreased, it remained elevated compared with normal control subjects (P < 0.05). Blood pressure, BMI, fasting lipid levels, smoking frequency, and use of hypolipidemic agents were unchanged. Mean carotid IMT was increased in pancreas transplant candidates but decreased by 1.8 ± 0.1 year after PTX (P = 0.0068), no longer different from that in normal control subjects or patients with type 1 diabetes.

CONCLUSIONS — Carotid IMT improves after successful PTX within 2 years of the procedure, with normalization of HbA1c and improved renal function, independent of changes in lipid levels, BMI, blood pressure, smoking, or use of hypolipidemic agents. This study suggests that CVD risk, future events, and mortality should improve after PTX in the absence of other significant, untreated CVD risk factors.

Diabetes Care 27:1706–1711, 2004

Cardiovascular disease (CVD) is the most common cause of mortality in patients with diabetes. Pancreas transplantation (PTX) normalizes glucose levels far better than any other strategy available for treatment of type 1 diabetes (1). Improvement in glucose levels reduces risk of microvascular complications in type 1 and type 2 diabetes and reduces macrovascular disease events in type 2 diabetes (2,3). Whether normalization of glucose can reduce CVD in type 1 diabetes, or whether PTX can reverse CVD in type 1 diabetes after it has occurred, is not as well established. Carotid intima-media thickness (IMT) correlates with risk and future CVD events. This is the first prospective study of carotid IMT in pancreas transplant recipients to determine whether PTX changes overall CVD risk.

RESEARCH DESIGN AND METHODS

PTX candidates
Patients with type 1 diabetes being evaluated for PTX who agreed to participate underwent baseline carotid ultrasonography at transplant evaluation and again at least 1 year after PTX if graft function was normal. Normal graft function was defined as HbA1c ≤ 6.5% (as defined by the clinical laboratory at the time of this study) and serum creatinine level ≤ 2.4 mg/dl. All PTX procedures were accomplished using whole-organ grafts with either bladder or enteric drainage of the exocrine duct and systemic venous drainage using the iliac vessels. At the time of post-PTX ultrasonography, cyclosporine-based immunosuppression was prescribed for 11 subjects and 14 subjects received tacrolimus-based immunosuppression.

Control groups
Candidates for PTX were frequency-matched for age to three groups: 1) patients with type 1 diabetes without significant nephropathy, as defined as normal serum creatinine level and urine albumin-to-creatinine ratio (< 30 μg/mg) (n = 20); 2) normal nonsmoking control subjects (n = 32); and 3) nondiabetic kidney transplant recipients (n = 16).

Outcome measures
BMI [(weight in kg)/(height in m²)], blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, ratio of total cholesterol to HDL cho-
HbA1c (%) 7.74
Smokers (%) 20 16 0.3173

years. HbA1c has been determined by medications, and immunosuppressant

25 25

sonography; post-PTX age was calculated at time of post-transplantation ultrasonography, and the remain-

DIABETES CARE, VOLUME 27, NUMBER 7, JULY 2004

Table 1—Demographic variables before and after PTX

<table>
<thead>
<tr>
<th></th>
<th>Pre-PTX</th>
<th>Post-PTX</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>25</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>41.4 ± 1.2</td>
<td>43.8 ± 1.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>25.9 ± 1.4</td>
<td>26.1 ± 0.9</td>
<td>0.1373</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.9 ± 0.8</td>
<td>26.1 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>149 ± 5</td>
<td>146 ± 4</td>
<td>0.6681</td>
</tr>
<tr>
<td>Diastolic</td>
<td>79 ± 3</td>
<td>79 ± 2</td>
<td>0.9739</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>20</td>
<td>16</td>
<td>0.3173</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.74 ± 0.42</td>
<td>5.14 ± 0.19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>4.52 ± 0.71</td>
<td>3.35 ± 0.07</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Data are means ± SE. Pre-PTX age was calculated at time of pretransplantation ultrasonography, duration of diabetes at the time of transplantation, and the remainder from the time of the pretransplantation ultrasonography; post-PTX age was calculated at time of post-transplantation ultrasonography, and the remainder of the values were from the time of the post-transplantation ultrasonography.

lesterol, HbA1c, serum creatinine, current medications, and immunosuppressant medications were assessed in all groups. A smoker was defined as smoking within 2 years. HbA1c has been determined by high-performance liquid chromatography (Tosoh Medics, San Francisco, CA) since November 1998. Before this, HbA1c was assayed using affinity chromatography (IsoLab, Akron, OH) (normal <8%), and these results were adjusted using a correlation equation determined when the assay was changed. Fasting lipid and serum creatinine levels were assessed in the clinical laboratory by standard methods.

Carotid ultrasonography

Both carotid arteries were examined using an ATL Ultramark 9 ultrasound system (Advanced Technology Laboratories, Bothel, WA) with a video recording of the distal 10–30 mm of the left and right common carotid arteries, as previously described (4). All images were analyzed by a single reader, who was blinded to the status or identity of the individual. Overall mean (mean ± IMT) and the mean of the maximum IMT of each view (mean-max IMT) were calculated. Interassay variation of repeated analysis of one normal and one PTX image presented randomly to the blinded reader was 3 and 2%, respectively. In 7 of 25 patients who underwent follow-up ultrasound more than once, the mean was calculated from all post-transplant ultrasonograms.

Statistical analysis

Paired Student’s t test was used to evaluate changes in carotid IMT mean and mean-max measurements between pre-PTX and post-PTX recipients, as well as to determine changes in continuous variables known to affect CVD risk before and after PTX. Correlation coefficients were used to evaluate whether each of the covariates (HbA1c, creatinine, each lipid variable, diastolic or systolic blood pressure, or BMI) were associated with changes in mean or mean-max carotid IMT. The F test in ANOVA was used to compare the post-PTX values with the three control groups: type 1 diabetic patients without significant nephropathy, nondiabetic kidney transplant recipients, and normal control subjects. If a significant difference was found between the four groups, Tukey’s test was used to determine which groups were significantly different from each other. P < 0.05 was considered significant.

RESULTS—CVD risk factors were studied prospectively before and after PTX (n = 25; Tables 1 and 2). Mean age at time of transplantation was 42.5 ± 1.2 years (mean ± SE). Most subjects (n = 18) underwent simultaneous pancreas-kidney transplantation, two subjects underwent PTX after kidney transplantation, and five subjects underwent only PTX. Mean daily dose of cyclosporine at time of carotid IMT was 342 ± 48 mg with concentration of 291 ± 50 ng/ml. Mean daily dose of tacrolimus was 7.1 ± 1.1 mg with concentration of 11.0 ± 1.1 ng/ml. All pancreas transplant recipients received prednisone (mean daily dose 6.8 ± 0.8 mg).

Mean and mean-max IMT pre- and post-PTX are shown in Fig. 1. Mean time post-PTX was 1.8 ± 0.1 year. Mean IMT decreased from 0.647 ± 0.019 (mean ± SE) to 0.602 ± 0.015 mm post-PTX, a 7% change (P = 0.0068). Mean-max IMT also decreased from 0.781 ± 0.027 to 0.704 ± 0.021 mm post-PTX, a 10% change from baseline (P = 0.0026).

HbA1c (P < 0.0001) and serum creatinine (P = 0.0002) decreased after PTX as expected, because most subjects underwent pancreas and kidney grafting, but there were no significant changes in blood pressure, BMI, smoking status, or fasting lipid levels (see Tables 1 and 2). There was also no significant change in use of lipid-lowering medications between pre-PTX and post-PTX (P = 0.65). However, mean IMT (P = 0.0410) and mean-max IMT (P = 0.0177) improved significantly after PTX, even when subjects taking hypolipidemic agents, either pre- or post-PTX, were excluded from analysis. Changes in carotid IMT after PTX were evaluated for any relationship to covariables. Systolic blood pressure correlated weakly with mean IMT (P = 0.0490) but not mean-max IMT (P = 0.0909). There was no significant correlation between IMT and diastolic blood pressure, HbA1c concentration, serum creatinine level, prednisone dose, use of tacrolimus versus cyclosporine, type of PTX, or CVD risk factors.

The characteristics of the control groups are shown in Table 3. These

Table 2—Lipid levels before and after PTX

<table>
<thead>
<tr>
<th></th>
<th>Pre-PTX</th>
<th>Post-PTX</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>199 ± 9</td>
<td>198 ± 7</td>
<td>0.9180</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>46 ± 4</td>
<td>50 ± 2</td>
<td>0.2666</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>124 ± 7</td>
<td>115 ± 5</td>
<td>0.2677</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>153 ± 12</td>
<td>141 ± 16</td>
<td>0.5222</td>
</tr>
<tr>
<td>Ratio of total to HDL cholesterol</td>
<td>4.72 ± 0.31</td>
<td>4.22 ± 0.26</td>
<td>0.0616</td>
</tr>
<tr>
<td>Patients receiving hypolipidemic agents (%)</td>
<td>12</td>
<td>6</td>
<td>0.6547</td>
</tr>
</tbody>
</table>

Data are means ± SE.
groups were compared with the PTX group (see Tables 1 and 2). There was no significant difference in age or sex distribution between the four groups. Average duration of diabetes in the PTX group at the time of transplantation was 25.9 ± 14 years, which was greater than in the subjects with type 1 diabetes (18.4 ± 2.2 years; P = 0.0049), even though they were the same age. The time since transplantation was 5.0 ± 1.0 years for post-kidney transplantation, longer than for post-PTX (1.8 ± 0.1 year; P < 0.01).

Mean and mean-max IMT were greater after PTX than after kidney transplantation in nondiabetic subjects (P < 0.05). However, IMT was not different after PTX from either normal or type 1 diabetic control subjects (Fig. 2). Age, sex, BMI, and smoking were not different between the groups. HbA1c in the post-PTX group was 5.14 ± 0.19%, the same as in the nondiabetic kidney transplant recipients and normal control subjects but less than type 1 diabetes (P < 0.05). Serum creatinine level improved to 1.35 ± 0.07 mg/dl after PTX and was similar to nondiabetic kidney transplant recipients but higher than type 1 diabetes and normal control subjects (P < 0.05). Systolic blood pressure after PTX was higher than after kidney transplantation or in type 1 diabetes or normal control subjects (P < 0.05). Diastolic blood pressure was lowest in type 1 diabetic control subjects, significantly lower than in pancreas or kidney transplant recipients or normal control subjects (P < 0.05).

Total cholesterol levels were higher in kidney transplant recipients than in type 1 diabetic or normal control subjects (P < 0.05) but were not different from those in post-PTX group. LDL cholesterol levels were higher in the nondiabetic kidney transplant recipients than in the type 1 diabetic control subjects (P < 0.05). Fasting triglyceride levels were higher in nondiabetic kidney transplant recipients than in type 1 diabetic or normal control subjects (P < 0.05) but were not different from those in the post-PTX group. Fasting triglyceride levels were also higher in the pancreas transplant recipients than in the type 1 diabetic control group (P < 0.05). HDL and the ratio of total cholesterol to HDL cholesterol were not significantly different between the groups. Therefore, although mean and mean-max IMT were greater after PTX than after kidney transplantation, the only CVD risk factor that might explain this difference is higher systolic blood pressure.

Of the 25 PTX recipients studied, one smoker later died of complications of pneumonia. Three nonsmokers experienced vascular events after PTX: one had a stroke and two underwent below-the-knee amputation.

**CONCLUSIONS** — PTX normalizes glucose, stabilizes or improves neuropathy, and reverses nephropathy (1). However, CVD events remain the primary cause of mortality in patients with type 1 diabetes and end-stage renal disease. Whether CVD risk or CVD improve or worsen after PTX could be the most important outcome. In the U.K. Prospective Diabetes Study, risk of CVD events in subjects with type 2 diabetes decreased with improved glucose levels (3), but the role of glucose in reducing risk of CVD events in subjects with type 1 diabetes is not as well established. After solid-organ transplantation, traditional CVD risk factors correlate with risk of CVD (5,6), although nontraditional factors may also contribute to CVD risk in this setting and require more study, such as immunosuppressant medications and inflammatory cytokines associated with rejection. Therefore, even though microvascular
companiments improve after PTX, it cannot be assumed that macrovascular disease will also improve.

Changes in specific CVD risk factors after transplantation can vary between individuals. Although glucose levels improve in subjects undergoing successful PTX procedures, lipid levels improve in many but not all subjects after PTX (1). Weight can be unchanged after PTX (7), but small increases are not uncommon over time, and at least one center reported a significant increase in weight after PTX, which is more likely in subjects with obesity before PTX (8). Blood pressure can vary with the immunosuppressive agent used (e.g., cyclosporine), the PTX procedure performed (e.g., bladder versus enteric drainage of exocrine duct), and weight changes after PTX.

Carotid IMT can evaluate the net impact of all changes, both positive and negative, in CVD risk factors and correlates with future CVD events and mortality. Carotid IMT has also shown to discriminate risk in type 1 diabetes. Carotid IMT was greater with age, male sex, triglyceride level, and albuminuria in one study (9) and with albuminuria, systolic blood pressure, endothelin level, urinary free cortisol level, and BMI in another study of patients with type 1 diabetes (10). At the conclusion of the Diabetes Complications and Control Trial, carotid IMT did not correlate with HbA1c, but did correlate with age and duration of diabetes, waist-to-hip ratio (men only), blood pressure, LDL cholesterol level, and smoking in univariate analysis and age, BMI, and smoking in multivariate analysis (11).

We have previously shown that candidates for PTX have greater carotid IMT than age-matched normal control subjects (12) and that carotid IMT was lower after PTX in a cross-sectional study (4). However, this is the first prospective study of carotid IMT in pancreas transplant recipients to show improved carotid IMT after PTX. HbA1c and creatinine improved over the same time interval, but there were no changes in blood pressure, BMI, smoking, lipid levels, or use of hypolipidemic agents to explain this change. A small unmatched subgroup did not benefit in improved carotid IMT, which might suggest that improved glucose is important to this change. There are few data on how kidney transplantation alone affects IMT in either diabetic or nondiabetic patients. The amount of change is similar to that described with changes in risk factors outside the transplant setting, such as the introduction of HMG CoA reductase inhibitors or thiazolidinediones (13–16).

The improvement in carotid IMT observed after PTX, consistent with the results of our recent cross-sectional studies, suggest that future vascular disease events and mortality should also be improved after pancreas-kidney transplantation. Most studies comparing vascular events and mortality evaluate changes after simultaneous pancreas-kidney transplantation in patients with type 1 diabetes receiving a cadaveric kidney transplant alone or simultaneous pancreas-kidney transplant candidates on the waiting list. In one study, the 7-year survival rate was higher and the acute myocardial infarction and CVD death rates were lower after simultaneous pancreas-kidney transplantation than in the other groups (17). In a similar study, simultaneous pancreas-kidney transplant recipients younger than 50 years had a higher 10-year survival rate than patients with type 1 diabetes on dialysis or type 1 diabetic patients receiving cadaveric kidney transplants (18). Simultaneous pancreas-kidney transplant recipients exhibit greater improvement in left ventricular ejection fraction, ratio of peak filling rate to peak ejection rate, and endothelial-dependent dilation of the brachial artery compared with recipients of kidney transplant only (19,20). However, comparison of CVD outcomes between these two groups must be viewed with caution because kidney transplantation alone is often performed over simultaneous pancreas-kidney transplantation in those with inadequate cardiovascular reserve.

However, other data support that simultaneous pancreas-kidney transplantation, in particular, improves CVD risk. Diastolic dysfunction is normalized 4 years after simultaneous pancreas-kidney transplantation (19,21). Progression of coronary artery disease, as determined by mean segment diameter loss on coronary angiography, was less in those with a functioning graft after simultaneous pancreas-kidney transplantation compared with those in whom the graft had failed (22). The present study shows that PTX improves or reverses one manifestation of CVD, carotid IMT, within 2 years, despite systemic hyperinsulinemia that accompanies systemic venous drainage, more rapidly than reported for reversal of nephropathy after solitary PTX (23).

However, successful PTX does not preclude eventual CVD progression with ongoing CVD risk factors, and not all mortality is related to CVD. Further vascular events (20) and progression of plaque (24) have been reported in simultaneous pancreas-kidney transplant recipients, especially smokers, and in those with worsening renal graft function and older age (24). Mortality after simultaneous pancreas-kidney transplantation

### Table 3—Control of group variables

<table>
<thead>
<tr>
<th>DM-1</th>
<th>Post-KTX</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>Age (years)</td>
<td>42.5 ± 2.3</td>
<td>41.3 ± 2.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.7 ± 0.6</td>
<td>19.4 ± 2.6</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>18.4 ± 2.2</td>
<td></td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>113 ± 3</td>
<td>133 ± 4</td>
</tr>
<tr>
<td>Diastolic</td>
<td>68 ± 1</td>
<td>81 ± 2</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.43 ± 0.25</td>
<td>5.35 ± 0.16</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.87 ± 0.03</td>
<td>1.42 ± 0.10</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>175 ± 8</td>
<td>219 ± 8</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>54 ± 23</td>
<td>50 ± 3</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>101 ± 7</td>
<td>132 ± 7</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>86 ± 8</td>
<td>183 ± 16</td>
</tr>
<tr>
<td>Ratio of total to HDL cholesterol</td>
<td>3.41 ± 0.22</td>
<td>4.53 ± 0.25</td>
</tr>
</tbody>
</table>

Data are means ± SE. See text for significant differences. DM-1, patients with type 1 diabetes but without significant nephropathy; KTX, nondiabetic kidney transplant recipients.
Carotid IMT after pancreas transplantation

has been reported to be better than after cadaveric kidney transplantation alone; however, mortality was not different after simultaneous pancreas-kidney transplantation than after living-donor kidney transplantation alone in two studies (18,25). Therefore, improvement in CVD events after simultaneous pancreas-kidney transplantation may still be offset by consequences of greater morbidity early after simultaneous pancreas-kidney transplantation, time on dialysis, or other unidentified differences between simultaneous pancreas-kidney transplant recipients and recipients of living-donor kidney transplant only. This study does not resolve the question of whether both a kidney and pancreas graft are necessary for improvement in IMT and important to understanding the relative role of resolution of renal failure versus euglycemia to improved vascular disease after transplantation.

In summary, this is the first prospective evaluation of carotid IMT in a cohort of successful pancreas transplant recipients. Carotid IMT, which correlates with future CVD events, is reduced after successful PTX. The change occurs rapidly, with improved glucose and renal function, but is independent of any significant changes in lipid levels, use of hypolipidemic agents, smoking cessation, blood pressure, or BMI. Because mortality after living-donor kidney transplantation alone is similar to simultaneous pancreas-kidney transplantation, it is important to determine whether differences in carotid IMT after living-donor and cadaver kidney transplantation can explain the differences in mortality compared with simultaneous pancreas-kidney transplantation.

Acknowledgments—This project was supported, in part, by the Nebraska Medical Center Clinical Research Center Research Support Fund and the Bly Endowment Research Fund.

We thank Janet Corr and Mary West for secretarial assistance in preparing the manuscript.

References