

# Pancreas Transplant Alone Can Improve Diabetic Nephropathy

Used alone, pancreas transplant restored normoglycemia, lowered proteinuria and had an overall positive effect on diabetic nephropathy.

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**D**iabetic nephropathy, the most common cause of end stage renal disease (ESRD), affects 25% to 45% of patients with type 1 diabetes. If a type 1 diabetic patient develops microalbuminuria, they have an 80% chance of progressing to overt nephropathy and a 50% chance of further progressing to ESRD within 10 years. Twenty years after the onset of microalbuminuria, 75% of type 1 diabetic patients will develop ESRD. In advanced grades, typical alterations of kidney structure include diffuse and nodular mesangial expansion and hyaline thickening of arterioles (Figures 1 and 2). Ultimately, developing diabetic nephropathy and also ESRD may lead to death.

Although pancreas transplant alone is not a therapy that will combat ESRD, it has positive effects on diabetic nephropathy when a patient's kidney function is still reasonable. This is especially true in patients whose urinary albumin excretion is increased. For type 1 diabetic patients with ESRD, transplantation therapy foresees the pancreas and the kidney.

Maintaining tight glycemic control will delay the onset of diabetic nephropathy, however if proteinuria persists and creatinine clearance declines, progression towards ESRD is ineluctable. To study the effects of pancreas transplant alone on restoring normoglycemia and other metabolic parameters and on the native kidneys, my colleagues and I conducted a study at the University of Pisa, Italy. We enrolled 32 type 1 diabetic patients scheduled to have pancreas transplant and measured their metabolic and kidney function by examining plasma glucose and plasma lipids, HbA1c, C-peptide, blood pressure, creatinine and creatinine clearance, and urinary protein excretion.

We reevaluated patient status 1 year after patients underwent transplantation, and paired them with 30 control type

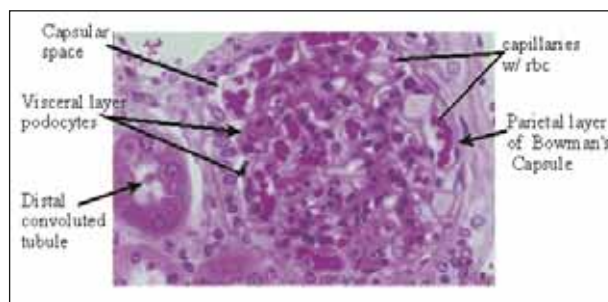


Figure 1. A normal kidney glomerulus.

1 diabetic patients who did not have pancreas transplantation. Baseline characteristics including sex, age, duration of diabetes and insulin dose were similar across the two groups. Results were compared using the Student's t test.

The data we have reported on is from the results at 1 year. Most of our patients have now been transplanted for 3 or more years, and they still have stable kidney function. Patients in the control group, however, have experienced a deterioration of kidney function. This suggests that the normalization of blood glucose, in addition to pancreas transplant alone, may stop the progression of nephropathy and actually may cause an improvement in function.

## TRANSPLANT TECHNIQUE

The pancreas was transplanted using a midline intraperitoneal approach and a portal-enteric drainage technique. Most patients who received transplant had persistent proteinuria.

The appearance of proteinuria signals kidney damage, and it contributes to deterioration of the function of the kidney. These changes may cause the kidney to poorly filter the blood, which leads to a rise in creatinine levels. Therefore, in

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this study we made sure to transplant the pancreas before creatinine levels were too high. The glomerular filtration rate in transplant patients was >50 mL/min.

We used 20 mg basiliximab at the time of transplant and again 4 days later. We also used tacrolimus (10 to 15 mg/mL during month 1, and 8 to 12 mg/mL thereafter), mycophenolate mophetil (1 to 2 g/day) and low-dose steroids. This was done to ensure that the pancreas would not be rejected, and in fact no patient in this study rejected the graft. One of the major areas of concern in this field is the possible toxicity of immunosuppressants on the kidney. However, the cocktail that we used was safe and patients did not experience negative side effects on the native kidneys.

One year after surgery, patients in the transplant group had improved health, and perfect graft function caused insulin independence. Fasting plasma glucose, HbA1c and C-peptide levels normalized (Table 1).

It appears that pancreas transplantation alone has a positive effect on albuminuria levels. Eight type 1 diabetic patients in the transplant group were normoalbuminuric before transplant and remained normoalbuminuric after transplantation. In the other transplant patients, albuminuria levels ranged from microalbuminuria (n=10) to macroalbuminuria (n=14). Four microalbuminuria and three macroalbuminuria patients attained normoalbuminuria after transplant.

All study participants had similar proteinuria at baseline (1.45 ±2.45 g/24 h, control group vs 1.20 ±2.44 g/24 h, transplant group). Although control patients did not experience a change in proteinuria after 1 year, a significant decrease in urinary protein was seen in those who received pancreas

**TABLE 1. METABOLIC DATA AT BASELINE AND AFTER 1 YEAR**

	Fasting plasma glucose (mg/dL)	HbA1c (%)	C-peptide (ng/mL)
<i>Nontransplanted</i>			
Baseline	212 ±89	8.4 ±1.5	0.02 ±0.00
1 year	188 ±88	8.0 ±1.3	0.02 ±0.00
<i>Transplanted</i>			
Baseline	250 ±105	9.0 ±2.0	0.01 ±0.00
1 year	85 ±10*	5.3 ±0.4*	2.7 ±1.1*

*Data are means ±SD. \*P <0.01 vs transplanted, baseline, and nontransplanted; †P <0.05 vs transplanted, baseline.*

transplant (0.67 ±1.58 g/24 h vs baseline,  $P < .005$ ).

The creatinine and creatinine clearance levels were similar between the control and transplant group (1.00 ±0.40 mg/dL and 84.4 ±28 mL/min vs 0.95 ±0.25 mg/dL and 95.4 ±30 mL/min, respectively) at baseline. Neither group experienced a significant change in the levels after 1 year.

As determined for the first time by our study, even alone, transplanting the pancreas results in improved diabetic nephropathy. Stabilization of normoalbuminuria, reduction of proteinuria and the unchanged creatinine clearance rates were byproducts of the operation. Furthermore, patients experienced an improvement in their blood pressure.

When pancreatic beta-cells release insulin, they also release C-peptide from the same upstream molecule. So, by restoring acceptable measures of endogenous insulin, C-peptide levels are also restored. There are some lines of evidence showing that C-peptide may benefit endothelial cells.

The conclusion that we have drawn from this study is that by restoring and sustaining normoglycemia, improving blood pressure and decreasing lipid levels, we are able to create a positive effect on kidney function in type 1 diabetes patients with acute diabetes.

The costs associated with ESRD – exceeding \$15 billion each year in the United States – are alarming. With effective methods of treating diabetic nephropathy, we may be able to combat the costs associated with this deadly complication. We believe that pancreas transplantation may be an effective method for obtaining positive kidney function results in type 1 diabetic patients. ■

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Coppelli A, Giannarelli R, Vistoli F, et al. The beneficial effects of pancreas transplant alone on diabetic nephropathy. *Diabetes Care*. 2005;28:1366-1370.

Image courtesy of Jim Swan



**Figure 2. A glomerulus in advanced diabetic nephropathy.**