'Bum' Pancreas Grafts Tied to Metabolic Syndrome

Better selection of donors can cut posttransplant incidence of metabolic syndrome, a study suggests.

BY JEFF EVANS
Senior Writer

Simultaneous kidney-pancreas transplant patients may be at risk for long-term kidney dysfunction if they continue to meet criteria for metabolic syndrome 1 year after the procedure, according to a prospective study.

The risk of long-term kidney dysfunction was especially high if patients had both metabolic syndrome and pancreas graft failure 1 year after transplantation. Poor selection of the pancreas graft or technical failures during surgery may contribute to pancreas graft loss and incomplete correction of metabolic syndrome in patients, according to surgeons who were interviewed.

In the study, Dr. Jeffrey Rogers, then at the Medical University of South Carolina, Charleston, and his colleagues used data from 241 insulin-dependent (mostly type 1) diabetic patients who were participating in a randomized, double-blind trial that tested different dosing regimens of daclizumab after simultaneous kidney-pancreas transplantation (Transplant. Proc. 2005;37:3549-51).

The incidence of metabolic syndrome in the patients decreased from 59% pretransplantation to 19% 1 year after the procedure.

But all of the patients could have potentially been free from metabolic syndrome had they received adequate pancreas grafts, Dr. David Sutherland said in an interview.

Two scenarios could explain why these patients developed metabolic syndrome, suggested Dr. Sutherland, director of the Diabetes Institute for Immunology and Transplantation at the University of Minnesota, Minneapolis. Some patients may have had a severe form of metabolic syndrome in which their insulin resistance or need for insulin was so high that even a normal pancreas could not have reduced their blood glucose level. Other patients may have had a form of metabolic syndrome that could have been reversed by receipt of a normal, healthy pancreas. Imperfect testing of deceased donors may be the reason these patients continued to have metabolic syndrome after transplant, he said.

Brain-dead donors on life support often have hyperglycemia because they receive drugs that raise blood glucose levels, such as steroids, Dr. Sutherland said. At the University of Minnesota, donors are given insulin so that hyperglycemia doesn't damage the beta islet cells of the pancreas. Donors who require hundreds of units of insulin to decrease their blood glucose level have extreme insulin resistance but may actually have a good pancreas, he said.

One can be more certain that donors who require 4 or 5 units of insulin to reduce their blood glucose level have a bad pancreas because the organ was not able to produce that amount of insulin itself.

Yet "most people think the opposite," Dr. Sutherland said. "If it takes 4 to 5 units for blood glucose to come down, they think, 'Oh, good, we'll use the pancreas.' Actually, that's the one I wouldn't use."

One can be "absolutely sure" that a pancreas is healthy when a donor does not need any insulin and has a normal blood glucose level despite the stress of brain death, he said.

Data on the donors were not provided in the current study.

Many of the donors were likely hyperglycemic when the organs were procured, and probably little attention was paid to how much insulin it would take to correct hyperglycemia in those donors, Dr. Sutherland surmised.

None of the patients with metabolic syndrome who developed pancreas graft failure at 1 year had a prior documented episode of kidney or pancreas rejection. Pancreas graft failure in these patients did not develop secondary to rejection of the organ.

"To me, that means that they got bum pancreases to begin with," Dr. Sutherland said.

In the study, the presence of metabolic syndrome in patients after 1 year was significantly associated with several changes 3 years after transplant, including decreased glomerular filtration rate, increased HbA_{1c} levels, a lower rate of pancreas graft survival, and a higher rate of acute pancreas graft rejection.

When rejection is diagnosed in one graft in simultaneous kidney-pancreas recipients, most of the time rejection is present in the other grafts as well, Dr. Rogers said in an interview. But in the current study, metabolic syndrome patients with and without pancreas graft failure at 1 year had similar rates of kidney rejection, which suggests that kidney rejection did not play a role in the difference in kidney function.

Early graft failure in metabolic syndrome patients probably resulted from thrombosis or other technical problems.

DR. ROGERS

Pancreas grafts probably failed early in patients with metabolic syndrome because of thrombosis or other technical problems, said Dr. Rogers, who is now in the surgery department at Wake Forest University, Winston-Salem, N.C.

Dr. Rogers suggested using low-dose anticoagulation postoperatively, and being cautious about using pancreases that are fatty, are from older donors, or are from donors who died of a stroke. ■

Benazepril Might Protect Kidneys in Advanced Renal Insufficiency

BY ROBIN SEATON JEFFERSON
Contributing Writer

Nondiabetic patients with advanced renal insufficiency showed evidence of renal protection from benazepril therapy, along with conventional antihypertensive treatment, reported Dr. Fan Fan Hou of the Nanfang Hospital of Southern Medical University in Guangzhou, China, and associates.

The investigators reported that they observed substantial renal benefits in patients with advanced (stage 4 chronic) renal insufficiency in a randomized, double-blind controlled trial of benazepril (N. Engl. J. Med. 2006;354:131-40).

ACE inhibitors have been shown to slow renal disease progression, but until now were limited to patients with serum creatinine levels of 3.0 mg/dL or less.

Based on the findings of the study, Dr. Hou and co-investigators suggested that treatment with ACE inhibitors be initiated at earlier stages of chronic kidney disease. ACE inhibitors have been shown to slow the progression of chronic kidney disease, but until now they have been limited to patients with serum creatinine levels of 3.0 mg/dL or less.

The 3-year study was conducted at the Nanfang (China) Hospital renal division. Patients were aged 18-70 years and had not received ACE inhibitors or angiotensin II–receptor antagonists for at least 6 weeks before screening. They had persistent proteinuria with serum creatinine levels of 1.5-5.0 mg/dL and creatinine clearance of 20-70 mL/min per 1.73 m^2, with variations of less than 30% in the 3 months before screening.

The study excluded patients if they had conditions such as renovascular disease, connective tissue disease, or obstructive uropathy, as well as patients being treated with corticosteroids, nonsteroidal anti-inflammatory drugs, or immunosuppressive drugs in the year preceding the trial.

The patients were divided into two groups: group 1 included patients with serum creatinine levels of 1.5-3.0 mg/dL, and group 2 consisted of patients with levels of 3.1-5.0 mg/dL.

During an 8-week run-in phase, patients were given benazepril 10 mg/day for 4 weeks with close monitoring. Then the dosage of the medication was increased to 10 mg twice a day for 4 weeks, and open-label antihypertensive agents were added as necessary.

After the run-in phase, benazepril was discontinued for 3 weeks. Antihypertensive agents were continued to control blood pressure.

After the 3 weeks, all patients in group 1 were given 10 mg of benazepril twice a day. Group 2 patients received either 10 mg of benazepril twice daily or placebo and antihypertensive agents.

"[The] primary efficacy measure was the time to the first event in the composite end point of a doubling of the serum creatinine level, end-stage renal disease or death," they said.

Of the 422 patients who participated in the run-in phase, 104 in group 1 and 112 in group 2 were assigned to benazepril 20 mg/day; another 112 in group 2 were assigned to placebo.

After a mean follow-up of 3 years, 107 patients assigned to benazepril in group 2 and 108 assigned to placebo were included in the efficacy analysis.

A total of 44 patients in group 2 assigned to benazepril reached the primary end point, compared with 65 patients on placebo.

Although all patients who received benazepril took the same dose, renal outcome was worse in group 2 than in group 1.

Benazepril treatment of the participants in group 2 resulted in a 43% reduction in the risk of reaching the primary end point, compared with placebo, and reduced the risk of end-stage renal disease by 40%. Also in group 2, benazepril was associated with reduced severity of proteinuria, compared with placebo, and was associated with a 23% reduction in the rate of decline in renal function.

Dry cough and an acute increase in serum creatinine level were reported mainly in the first 2 months of benazepril therapy. The incidence of hyperkalemia in group 2 was similar for patients who received benazepril and those who received placebo.

In an editorial comment accompanying the report, Dr. Lee Hebert of Ohio State University, Columbus, wrote that "although their results indicate that it may be time to change our practice, a number of caveats should be considered before we do so" (N. Engl. J. Med. 2006;354:189-91).

He said that the researchers used only half the maximal recommended dose of benazepril for patients with chronic kidney disease, as well as a twice-daily regimen that provides little opportunity for nocturnal recovery from any hyperkalemia.

Dr. Hebert added that although the results of the study support the continuation of the ACE inhibitor benazepril for treatment of chronic kidney disease, whether other types of ACE inhibitors would achieve the same results is not clear. ■

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