BYRON J. HOOGWERF, MD, EDITOR

Pancreas transplantation: state of the art

SHARON GRUNDFEST-BRONIATOWSKI, MD

■ Improvements in technique and in the diagnosis of rejection have led to progressively better pancreas transplant graft and patient survival rates over the past 5 years. Refinements in organ preservation are making it easier for centers to share organs, with better immunologic matching and therefore additional improvement in results. As new immunosuppressive agents become available, pancreas transplantation may be an option for diabetic patients early in the course of their disease, before secondary complications become disabling.

□ INDEX TERMS: TRANSPLANTATION, PANCREAS □ CLEVE CLIN J MED 1990; 57:564-570.

MORE THAN 50 NEW cases of insulin-dependent (Type I) diabetes mellitus (IDDM) per million population are diagnosed each year in the United States, and the incidence of the disease is increasing. The complications of the disease and the associated damage to quality of life make the disease a major public health problem. At least half of patients with diabetes will suffer serious complications such as renal failure, blindness, heart disease, stroke, and neuropathy; furthermore, these patients are at increased risk of infection and episodes of ketoacidosis or insulin overdosage.[1]

See Hoogwerf (p 563).

The development of exogenous insulin therapy extended the diabetic patient's life expectancy from several weeks or months to about 20 years from the time of diagnosis.[2] Renal dialysis and renal transplantation were two other significant strides in the management of these patients. Diabetic patients with untreated, persistent proteinuria survive a mean of 7 years, and the major cause of death is renal failure.[2] The mortality rate for IDDM patients during the first 2 years of renal failure is more than 25%.[3] Although dialysis saves lives, the survival rates for diabetic patients on dialysis are not as good as those of nondiabetic patients on dialysis.

RENAL TRANSPLANTATION PROBLEMS

Early attempts at renal transplantation in the presence of IDDM had poor results, with a 1-year mortality of 40% and only 25% of grafts functioning at the end of 3 years.[4,5] Recently, however, kidney transplantation has become almost routine for diabetic patients; the 5-year survival rate is 85% or better and quality of life is improved compared to dialysis.[6-8]

These are encouraging figures, but the sobering facts are that at least half of diabetic patients are already legally blind and most have severe retinopathy at the time of evaluation for a kidney transplant.[9] Most have

From the Department of General Surgery, The Cleveland Clinic Foundation.

Address reprint requests to S.G.-B., head, Section of Pancreas Transplantation, Department of General Surgery, Desk A110, The Cleveland Clinic Foundation, One Clinic Center, 9500 Euclid Avenue, Cleveland, Ohio 44195-5043.

some degree of peripheral neuropathy. Heart disease, hypertension, impotence, autonomic neuropathy, and orthostatic hypotension are also common.

Renal transplantation alone does little to improve metabolic control; indeed, the steroids used for immunosuppression often increase insulin requirements, and serum cholesterol frequently rises.[10] Although symptoms of neuropathy may temporarily improve or stabilize, small-vessel disease eventually worsens and takes its toll. Diabetic lesions can be seen histologically in the transplanted kidney within 2 years after operation; however, other diabetic complications will usually cause problems before the nephropathy becomes clinically significant.[11,12] In one early series, 50% of diabetic transplant recipients who survived 1 year required a major amputation.[13]

ONE SOLUTION: PANCREAS TRANSPLANT

Pancreatic transplantation is the only treatment now available that provides consistent blood glucose control for patients with IDDM. Kelly and Lillehei performed the first human pancreas transplants at the University of Minnesota in 1966, when immunosuppression was relatively poor by today's standards.[14] Of 14 grafts which they performed over 1 year, only one functioned for more than a year; but in all patients, normal carbohydrate metabolism was achieved while the grafts functioned. Complications included hemorrhage, infection, and rejection.

Discouraged by the poor results of whole-organ and segmental-organ grafting, Ballinger and Lacy began performing islet cell transplants in animals in the early 1970s.[15] They demonstrated that syngeneic islets will survive in the liver, spleen, kidney capsule, and peritoneum in rats, and found that approximately 500 islets were needed to normalize blood glucose and insulin levels. In animals, islet transplants prevented hyperglycemia, reestablished normal urine volume, and reduced complications such as cataracts, neuropathy, retinopathy, and nephropathy.

The situation is more complex in humans. Despite multiple attempts, there are no reported cases of patients achieving long-term freedom from supplemental insulin injections after allogeneic islet cell transplants.[16,17] Recently, there has been some interest in the use of cultured human fetal pancreatic tissue. This technique produces some insulin, but normoglycemia has not been reported in these patients.[18] Furthermore, there are ethical concerns about the use of fetal tissue.

The introduction of cyclosporine encouraged surgeons to again try vascularized pancreatic grafting, and the number of such operations has increased exponentially since 1978. Some 400 pancreas transplants are performed annually in nearly 90 centers around the world,[8,19–25] and more than 2,000 operations have been done.

The 1-year actuarial graft survival rate has improved through the years: success rates calculated by the International Pancreas Transplant Registry were 5% for all cases performed from 1966 through 1977, 26% for 1978 through 1983, 40% for 1984 through 1985, and 56% for 1986 through 1988.[19]

In patients who undergo simultaneous kidney and pancreas transplantation, kidney graft survival rates equal those of diabetic patients who undergo renal transplantation alone, but rejection is more common than after renal transplantation alone.[8,23] The double transplant procedure is associated with a higher postoperative complication rate than is renal transplantation, and patients who undergo the double procedure spend more time in the hospital during the first postoperative year.[8,22–25,26] On the other hand, several authors have reported that quality of life, health, and long-term rehabilitation, such as return to work and physical activity, are better after combined pancreas-kidney transplantation than after kidney transplants.[20,27,28] It is too early to tell what impact the double transplant will have on life expectancy.

SELECTING CANDIDATES

Diabetes is not an immediately life-threatening illness in the way that liver failure or cardiomyopathy may be. Nevertheless, diabetic patients with end-stage renal disease (ESRD) are severely incapacitated, and many are at high risk of complications from anesthesia and surgical stress.

When pancreatic transplants were considered experimental, most centers performed them in combination with renal transplantation only in diabetic patients with end-stage renal disease. Since these patients would receive immunosuppression for their renal grafts, it was thought that the technical details of the pancreas transplant could be achieved with minimal additional risk.

Option for pre-uremic patients

Improvements in immunosuppressive therapy and surgical results have made it reasonable to consider pancreas transplantation for pre-uremic patients (*Table 1*), although this issue is far from resolved. Animal experiments indicate that diabetic complications can be totally avoided if normal carbohydrate metabolism can be restored soon after the onset of disease. Early intervention will prolong survival,

TABLE 1
INDICATIONS AND CONTRAINDICATIONS FOR PANCREAS TRANSPLANTATION

Indications
Combined kidney-pancreas
Type I diabetes with end-stage renal disease
Pancreas alone
Type I diabetes with a functioning renal transplant or with one or more of the following:*
Pre-uremic nephropathy (albuminuria with creatinine clearance > 50 mL/min)
Progressive retinopathy
Brittle diabetes
Marked insulin resistance
Severe neuropathic pain
Pancreatectomy for benign disease
Contraindications
Drug abuse
Psychosis
Concurrent malignancy or infection
Ongoing peripheral gangrene
Incapacitating neuropathy (bedridden)
Incapacitating gastropathy (unable to take oral medication)
Severe coronary artery disease or cardiomyopathy

* These criteria are not routinely used in all institutions doing pancreas transplantation

provided that the complications of the immunosuppression are less disabling than those of diabetes. Unfortunately, cyclosporine, one of the most commonly used immunosuppressive agents, is associated with decreased renal blood flow and significant nephrotoxicity. In a patient with a borderline kidney, these effects may negate the stabilizing influence of a pancreas transplant.

Graft survival rates are lower when pancreas transplants are carried out in the absence of simultaneous kidney transplants. Factors that contribute to the lower survival rates include the immunocompetence of the nonuremic patient and the difficulty in early diagnosis of pancreatic graft rejection.[8,19,29] The availability of newer immunosuppressive medications could well improve the outcome of single pancreatic transplants in the near future.

Preoperative workup

The preoperative history and physical examination should give special attention to possible cardiac disease. An electrocardiogram and thallium stress test will exclude ischemic heart disease. The diagnosis of type I diabetes is confirmed with measurements of blood glucose and C-peptide.

Specialists are involved in the workup; ie, an ophthalmologist performs the retinal examination and fluorescein angiography; and a nephrologist evaluates the kidneys, with measurements of creatinine clearance, protein excretion, and bladder capacity, and, when necessary, renal biopsy.

Peripheral neuropathy is evaluated with nerve conduction times and electromyograms, and autonomic neuropathy by gastric emptying studies. The peripheral vasculature is assessed, along with supine and standing blood pressures.

All candidates for pancreas transplant undergo HLA antibody testing and serological studies for hepatitis, cytomegalovirus, and herpes simplex. Psychosocial counseling also is indicated to make sure that the patient understands the ramifications of the operation and that adequate support is available at home.

DONOR POOL INCREASING

Most pancreatic grafts in the United States are obtained from cadaver donors. Donors with a history of diabetes, sepsis, cancer, communicable disease (except CMV virus), alcohol abuse, gastrointestinal trauma, or significant hemodynamic instability are excluded.

Several centers have experimented with hemipancreatectomy in living related donors. Technically, this procedure is somewhat more risky because of the higher rate of vascular thrombosis when the splenic artery is used instead of the celiac or superior mesenteric trunk. There is also some concern about the metabolic effects of hemipancreatectomy on the donor.[30–32] The aftereffects of this major operative procedure include decreased tolerance for glucose loads and decreased fat absorption from the intestine.

Before 1988, most centers limited cadaver grafting to organs that had less than 6 hours of cold ischemic time. This made prospective HLA matching impossible, but allowed routine crossmatching of donor lymphocytes to reduce the risk of accelerated rejection. Solutions are now available that allow preservation times of up to 30 hours.[33–35] Organ sharing between institutions and better HLA-DR matching will probably occur in the near future.

Unlike kidney, heart, and liver transplants, pancreatic transplantation is not currently covered by Medicare, although some private insurers do cover the costs.

TECHNICAL ISSUES

Four issues must be addressed when planning a pancreas transplant procedure: (1) handling of pancreatic digestive enzymes, (2) placement of venous drainage, (3) the amount of pancreatic tissue transplanted and its blood supply, and (4) prevention of postoperative thrombosis.

Pancreatic secretions

The pancreas produces not only insulin, but also exocrine secretions that are drained into a hollow viscus. Some surgeons obliterate the exocrine pancreas by injecting the pancreatic duct with a rubber polymer or an absorbable amino acid compound. Many groups that initially used the duct injection technique have given it up because of pancreatic fistula formation and impaired ability to monitor graft function.

Most US surgeons drain the exocrine secretions into the bladder; the intestine, stomach, and gallbladder have also been used. Although intestinal drainage is more physiologic, it exposes the immunosuppressed patient to a higher risk of infection than does urinary drainage. Urinary drainage also allows monitoring of pancreatic function by urinary amylase and pH, which signal rejection earlier than does hyperglycemia.

Venous drainage

It has been suggested that paratopic placement of the pancreas with a splenic vein-to-splenic vein anastomosis and pancreaticogastrostomy is more physiologic than orthotopic placement in the iliac fossa. Paratopic placement ensures delivery of insulin directly to the liver through the portal vein, and avoids systemic hyperinsulinemia.[36] However, portal venous drainage has no major advantage over systemic drainage in control of blood sugar levels and prevention of diabetic complications.[37] Furthermore, this technique has been associated with a high rate of vascular thrombosis, probably because of the technical difficulties of the venous anastomosis and the relatively low flow rates in segmental grafts.[20] At present, all major centers prefer placing the graft in the iliac fossa because it is technically easier.

Whole *v* segmental grafting

Most US surgeons prefer whole pancreas transplantation over segmental grafting, even though total pancreatectomy is a more difficult and time-consuming operation in the donor than is segmental resection. Also, the need to share organs with a liver transplant team sometimes necessitates the use of vascular reconstructive techniques by the pancreas team. On the other hand, use of the whole organ provides a larger reserve of islet cells. This is helpful during rejection episodes, when islet cells may be damaged. It also is somewhat easier to anastomose a segment of attached duodenum to the bladder or to the intestine than it is to perform a pancreaticocystostomy or pancreaticojejunostomy, and there is less chance of a leak.

Postoperative thrombosis

The pancreas has a notoriously precarious blood flow and is susceptible to ischemic injury and postoperative pancreatitis. Because pancreatic vessels are small, blood flow resistance is high compared to organs such as the kidney. This situation may be worsened by postoperative swelling of the gland and release of thromboxane A_2. Furthermore, diabetic patients have hypercoagulability with an increased tendency toward platelet aggregation, possibly because of lower levels of plasma antithrombin III.[38]

Strategies to combat thrombosis have included formation of an arteriovenous fistula between the splenic artery and splenic vein, inclusion of the spleen with the graft, and anticoagulation therapy,[39-41] but none of these has been completely successful. Indeed, transplantation of the spleen is condemned because it induces graft-*v*-host disease.[42]

Thrombosis appears to be somewhat less frequent when the whole organ is used, and the newer preservation solutions have decreased the incidence of postoperative pancreatitis.

DIAGNOSIS OF REJECTION

Pancreatic rejection is more difficult to diagnose than liver, kidney, or heart transplant rejection. Rejection may mimic infection and graft pancreatitis. Clinical signs such as fever, ileus, and graft tenderness are unreliable. The blood glucose may be affected by stress, glucocorticoids, and infection; furthermore, blood sugars may remain normal until up to 90% of insulin-producing cells are destroyed.

The most commonly used test for bladder-drained grafts is measurement of urinary amylase levels. Although there is great variation, levels below 10,000 IU/L in a previously normally functioning graft are usually significant and suggest rejection. In the past, needle biopsy of the pancreas was avoided because of the potential for pancreatic fistula, but several groups have recently reported success with fine-needle techniques. Aspiration cytology appears to be useful, as do percutaneous and trans-cystoscopic biopsy techniques.[43-45]

Other tests for pancreatic rejection include: measurements of C-peptide, interleukin-2 receptors, pancreas-specific protein, urinary pH, insulin, trypsin, and pancreatic juice volume. Examination of the juice for inflammatory and blast cells also is used, as well as imaging studies such as radionuclide flow scans (eg, DTPA), angiography, and magnetic resonance.[46-49]

Simultaneous kidney transplantation permits earlier

diagnosis of rejection because serum creatinine is a reliable marker.[8] Rejection usually involves both organs when they are from the same donor. On the other hand, because the kidney presents a larger amount of foreign antigen to the host, it may protect the smaller graft from rejection. Rejection in the two organs is not necessarily concurrent. For example, if the kidney rejects first, there is usually evidence of pancreatic rejection within a few weeks. If the pancreas rejects first, the kidney has a high chance of succumbing to chronic rejection within the following 2 years.

IMPROVING RESULTS

The goals of pancreas transplantation are improved survival and quality of life, reduction of future complications from diabetes, and possibly, amelioration of existing complications. There is no question that the patient's quality of life improves following pancreas transplantation.[27,28,50]

Graft and patient survival rates are also improving. Registry statistics for pancreas-kidney transplants performed between 1986 and 1989 show 1-year actuarial graft survival rates of 56% and patient survival rates of 87%.[19] Graft survival rates for simultaneous kidney-pancreas transplants are significantly better (56%) than for pancreas transplantation after kidney transplantation (42%) or for pancreas transplantation alone (32%).[19]

Among diabetic patients who received combined kidney and pancreas grafts from 1984 through 1988, the kidney graft survival rate was 72% at 1 year—a figure comparable to the graft survival rate among diabetic patients who received only cadaver renal grafts. Selected series of combined kidney and pancreaticoduodenal transplantation show 1-year pancreatic graft survival rates of greater than 80% and renal graft survival rates higher than 90%.[22,51]

Recent analyses suggest a better chance of success with whole-organ bladder-drained grafts than with other techniques.[19] Common complications of bladder drainage include early and late bladder leak, bleeding, infection, urinary tract infections, and a need for bicarbonate supplementation to prevent metabolic acidosis.

Most groups today achieve immunosuppression with long-term steroid-sparing regimens of cyclosporine and azathioprine, along with prednisone. A short postoperative course of anti-lymphoblast globulin (ALG) or OKT-3 is also frequently used, although the benefits of these drugs have not been conclusively demonstrated.[19,23,52–54]

Glucose metabolism

Extensive investigations of the long-term metabolic control provided by pancreatic transplantation show that transplantation often normalizes glucose metabolism; however, serum insulin and plasma glucagon levels are generally higher than in normal controls.[54–58] Mean 24-hour levels of free fatty acid, 3-hydroxybutyrate, and alanine are also similar to those in normal subjects. Ostman and colleagues have shown that the hyperinsulinemia is not merely the result of systemic delivery, but is at least partly due to increased insulin resistance.[58] Growth hormone, which is usually abnormally high in diabetic patients, normalizes after pancreas transplantation.[58]

Neuropathy

The effects of pancreas transplantation on the complications of diabetes are still being evaluated. Nearly all groups have reported alleviation of peripheral neuropathy as measured by nerve conduction times, but renal transplantation alone will ameliorate symptoms temporarily in many patients.[59,60] Alleviation of autonomic neuropathy has been reported, but not conclusively demonstrated.[61]

Microcirculation

The Munich group has shown improved microcirculation in the extremities.[62] These authors also found that visual acuity improved in 56%, stabilized in 32%, and deteriorated in 12% of patients. Konigsrainer and his colleagues also have reported a beneficial effect of pancreas transplantation on retinopathy.[63] On the other hand, Ramsay and colleagues, following a group of patients who had functioning native or transplanted kidneys at the time of pancreatic grafting, found no difference in retinopathy for the first 3 years. After that, however, retinopathy deteriorated in the hyperglycemic group and appeared to stabilize in the euglycemic group.[64,65] It appears that pancreatic transplantation may stabilize or ameliorate early retinopathy, but will not reverse proliferative changes.

Nephropathy

Successful pancreas transplantation protects the renal glomeruli from damage. Bilous and colleagues recently reported that recipients of pancreas transplants had smaller glomerular volumes and less mesangial expansion than did matched diabetic patients who underwent renal transplants alone.[66] Further, pancreas transplants following a successful kidney graft halted the progression of glomerular disease.

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