

# Pancreas and Islet Transplantation for Patients With Diabetes

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Historically, patients with diabetes have expended tremendous effort in pursuing a return to normoglycemia. The relatively recent results of the Diabetes Control and Complications Trial (DCCT), demonstrating an approximate 50% reduction in eye, nerve, and kidney complications in a group of patients receiving intensive treatment for hyperglycemia (1), have made this pursuit even more intense. Successful pancreas and islet transplantations are currently the only therapies that reproducibly achieve normoglycemia by reestablishing endogenous insulin secretion responsive to normal feedback regulation. This report briefly considers the history, techniques, clinical results, and risk-benefit relationship of successful pancreas and pancreatic islet transplantations in hyperglycemic patients with long-standing diabetes.

**PANCREAS TRANSPLANTATION** — Pancreatic transplantation was first used for the treatment of type 1 diabetes in humans in 1966 (2). In that early era, the rates of graft and patient survival were low, so very few procedures were performed until 1978. Important steps toward improving surgical results included the introduction of improved immunosuppressive regimens, especially the use of cyclosporine and anti-T-cell

agents, new surgical techniques, and the selection of healthier recipients. In the past decade, the number of procedures performed has steadily increased each year (3).

By the end of 1997, nearly 10,000 pancreatic transplantations had been recorded in the International Pancreas Transplant Registry, and in that year alone, more than 1,200 procedures were reported. The results from different centers vary depending on operative experience and patient selection. The 1994–1997 data from the International Pancreas Transplant Registry (3) indicate an overall 1-year patient survival rate of >90% (Fig. 1). The 1-year rate of graft survival (defined as total freedom from insulin therapy, normal fasting blood glucose concentrations, and normal or only slightly elevated HbA<sub>1c</sub> values) was 82% when a pancreas and a kidney were transplanted simultaneously (SPK), 71% when a pancreas was transplanted after kidney transplantation (PAK), and 62% when a pancreas was transplanted alone (PTA).

Most pancreatic transplantations in diabetic patients with renal failure are performed at the same time as or after kidney transplantation. The objectives in this instance are to render the patient free of exogenous insulin therapy, to arrest the progress of ongoing secondary complications, to protect the transplanted kidney from hyperglycemia, and to improve qual-

ity of life. In unusual circumstances, the pancreas is transplanted alone, but the decision to do so is more difficult. In these patients, kidney transplantation and immunosuppression are not already indicated, and survival of pancreas grafts when transplanted alone is lower than when transplanted simultaneously with a kidney. Inclusion criteria for PTA include that the patient is severely metabolically unstable, has severe autonomic dysfunction, or generally has a very poor quality of life because of the effects of chronic diabetes. Although the success rate of PTA is lower, this may be due to the lack of a marker for pancreas rejection that is as sensitive as serum creatinine is as a marker for kidney transplant rejection. Hence, rejection is more difficult to detect and anti-rejection treatment is initiated later.

## Technique

Most pancreatic grafts are from cadaver donors, and venous drainage of the pancreatic graft is conventionally through a vein that drains into the systemic rather than the portal circulation. Less commonly, a segment of pancreas is donated by a living related donor who is willing to undergo a hemipancreatectomy. Despite a diversity of protocols, most pancreatic transplants are performed with quadruple immunosuppression with antibody induction therapy with either a monoclonal or polyclonal agent. Maintenance immunosuppression is triple therapy with a calcineurin inhibitor (cyclosporine or tacrolimus), an antimetabolite (mycophenolate mofetil or azathioprine), and corticosteroids. With the availability of new immunosuppressants, some centers are performing pancreas transplants without antibody induction. Furthermore, rapid tapering of steroids with subsequent withdrawal is also being investigated. Although these immunosuppressive regimens are complicated, diabetic patients usually consider them easier to manage and less demanding than continued diabetes with hyperglycemia and insulin-based management.

In the most common scenario, a total pancreas still attached to a small portion of the donor duodenum containing the exit of the pancreatic duct is used. The pan-

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Abbreviations: DCCT, Diabetes Control and Complications Trial; PAK, pancreas after kidney transplant; PTA, pancreas transplant alone; SPK, simultaneous pancreas and kidney transplant.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

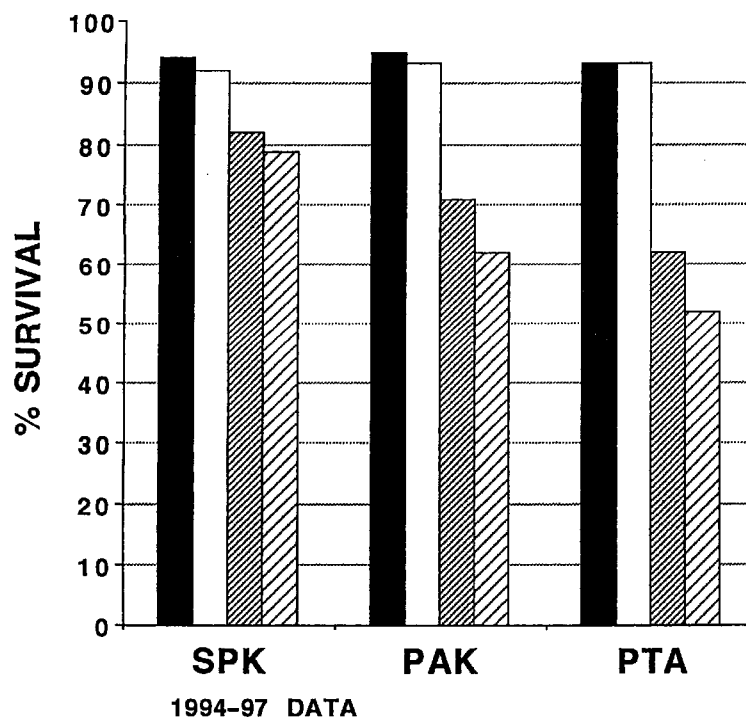


Figure 1—Comparison of 1- and 3-year patient and graft survival rates for SPK, PAK, and PTA according to the International Pancreas Transplant Registry (3). ■, 1-year patient survival; □, 3-year patient survival; ▨, 1-year graft survival; ▩, 3-year graft survival. Adapted from Robertson RP: Pancreas and islet transplants for patients with diabetes: taking position and making decisions. *Endocr Pract* 5:24–28, 1999.

creas is placed laterally in the pelvis and provided with arterial flow from the iliac artery and venous return via the iliac vein. The duodenal segment and pancreatic duct outlet are oversewn onto the urinary bladder, which receives the exocrine drainage. Alternative modifications to this approach include enteric rather than bladder drainage of the exocrine pancreas and portal rather than systemic drainage of the endocrine pancreas. Advantages of bladder over enteric drainage are the use of urinary amylase to monitor for rejection and the avoidance of small-bowel complications such as obstruction and infection. Advantages of enteric over bladder drainage are avoidance of urinary bladder complications such as urinary tract infection, hematuria, and reflux pancreatitis. A theoretical advantage of portal over systemic venous drainage of the transplanted pancreas is the avoidance of hyperinsulinemia caused when systemic drainage bypasses hepatic metabolism of insulin secreted by the allograft. In all variations, the choice of procedure is independent of whether or not a kidney is transplanted into the pelvic area and the native pancreas is left untouched.

#### Acute and chronic rejection

A transplanted graft can be rejected within days or after years of successful transplantation. The reasons for this variable response are many, but the management is the same, i.e., hospitalization and intensive acceleration of immunosuppression. Detection of pancreas rejection is made easier when a kidney has also been transplanted, because an increase in serum creatinine can be easily monitored and used as a signal that both organs are undergoing a rejection episode. In PTA with bladder drainage, the less sensitive indices of decreasing urinary amylase (from the donor exocrine pancreas), increasing serum amylase, and increasing blood glucose levels are the only available warnings. When suspected, cystoscopic transduodenal or percutaneous biopsy with ultrasound guidance is used to confirm rejection. Although instances of autoimmune attack have been suggested, this is probably an unusual cause of allograft rejection, in part because the recipient receives immunosuppressive drugs that are known to suppress primary autoimmune responses fairly effectively.

#### Metabolic results

Successful pancreatic transplantation results in independence from exogenous insulin therapy, normal blood glucose concentrations, and normal or near-normal HbA<sub>1c</sub> values (4). These beneficial effects on glucose regulation are the result of restoring pancreatic islet function. The patients have normal insulin responses to oral and intravenous glucose stimulation as well as to intravenous arginine and intravenous secretin (4–15). The basal and stimulated peripheral serum insulin concentrations are two to three times higher than normal. This hyperinsulinemia is due in part to insulin resistance caused by prednisone therapy, but it is more greatly due to the systemic venous drainage of the allograft (6), which allows the secreted insulin to circumvent first-pass hepatic degradation of the hormone. Normally, insulin is secreted into the portal vein, and 50–90% of the insulin in portal venous blood is taken up and degraded by the liver. Whether posttransplantation hyperinsulinemia has adverse effects, for example on atherosclerosis, is not known. However, serum triglyceride and LDL cholesterol concentrations fall and serum HDL cholesterol concentrations rise in pancreatic transplant recipients (16–18).

Glucose counterregulation after hypoglycemia is also improved by pancreatic transplantation (18–21). This is an important benefit because patients who have had diabetes for many years, as have most patients undergoing pancreatic transplantation, typically have abnormal glucose counterregulation due to decreased glucagon and epinephrine responses to hypoglycemia. The improvement in glucose counterregulation after insulin-induced hypoglycemia in recipients of pancreatic transplants is due to normalization of the glucagon counterregulatory response and improvement in the epinephrine counterregulatory response (18–21). Importantly, symptom recognition of hypoglycemia is normalized (21). Hypoglycemia as a complication of pancreas transplantation has been reported (22), but it is usually mild (23).

In both cross-sectional and prospective studies, the posttransplantation improvement in glucose metabolism, HbA<sub>1c</sub> values, acute insulin responses to intravenous glucose, and counterregulatory responses of glucagon and glucose to insulin-induced hypoglycemia have been documented to be maintained for up to 5 years (24), and success for 10–20 years is common in some centers.

Effects on the chronic complications of diabetes

The impact of successful pancreas transplantation and normalization of glycemia on the secondary complications of diabetes has been studied extensively. No randomized trials of pancreas transplantation versus intensive insulin-based management have been performed; rather, historic controls or case-controlled designs have been used. The favorable results of the DCCT are often cited to support the hypothesis that normalization of glycemia by pancreas transplantation should have a beneficial effect on the chronic complications of diabetes. Renal structure benefits have been found, as reflected by diminished mesangial mass in patients receiving SPK versus those receiving a kidney alone (25,26) and by improvement in native renal structure 10 years after successful PTA (27). Improvement of motor and sensory nerve conduction velocities has been demonstrated in recipients (28–34) with partial reversal of neuropathy observed 10 years posttransplant (28). Importantly, life expectancy in patients with autonomic insufficiency has been reported to be significantly increased (33). Quality of life studies consistently demonstrate benefits such as return to work and successful pregnancies (35–37). However, no beneficial effects have been demonstrated for established retinopathy (38–40) or for abnormalities of gastric motility (30,32). It is currently unknown whether pancreas transplantation has any effect on macrovascular disease associated with diabetes. SPK has been shown to improve fasting lipid profiles and blood pressure (17,41) without changing body weight in most patients, which might be expected to improve atherosclerotic vascular risk. Importantly, these studies of secondary complications of diabetes must be interpreted in light of the fact that most patients undergoing pancreas transplantations have already had the disease for more than 2 decades. Trials of pancreas transplantation much earlier in the course of diabetes are being considered to determine whether maintenance of normal levels of glycemia and HbA<sub>1c</sub> can prevent secondary complications altogether.

#### Risks and cost-benefit analyses

Risks associated with pancreas transplantation include clinical complications caused by the surgery and by chronic immunosuppressive drugs, as well as death. Perioperative complications leading to relaparotomy

occur in ~30% of patients and include intra-abdominal infections and abscess, vascular graft thrombosis, anastomotic leak, and duodenal stump leak (42). Drug-related complications include bacterial and viral infections (particularly cytomegalovirus) and malignancy (particularly skin tumors and lymphoma) secondary to chronic immunosuppression. The malignancy risk is <1% and is no worse for pancreas transplantation patients than it is for recipients of other organs. Other drug-related complications include osteoporosis and insulin resistance (steroids) and decreased renal and pancreatic  $\beta$ -cell function (cyclosporin, tacrolimus). The mortality rate 1 and 3 years after PTA, SPK, or PAK, is ~7% (3). The majority of deaths are due to cardiovascular disease and usually occur more than 3 months after discharge from the hospital. The mortality rate 1 year after the much less invasive procedure of pancreatic islet transplantation is 5% (43). Thus, it seems likely that the mortality rates are related more to chronic diabetes than to pancreas transplantation itself. Initial concerns that mortality after SPK is greater than that after kidney transplantation alone (44) have not been substantiated in subsequent studies (3,45).

Very few studies comparing the costs and benefits of pancreas transplantation versus insulin-based management of diabetes have been published. However, a recent study concluded that SPK, when adjusted for quality of life, is more cost-effective for diabetic patients with end-stage renal disease than is kidney alone transplantation or hemodialysis (46).

#### ISLET

**TRANSPLANTATION** — The less invasive procedure of islet transplantation in humans with diabetes would be expected to be safer and much less costly than pancreas transplantation. However, this procedure also requires lifetime immunosuppression with drugs. Much effort and enthusiasm have been expended to establish techniques to maximize the yield and quality of islets isolated from various sources. Unfortunately, transplantation of islet allografts usually fails, although there is continued optimism and a few notable instances of prolonged success (46–49). Interestingly, such patients fail to secrete glucagon from their native  $\alpha$ -cells in response to hypoglycemia despite the reestablishment of euglycemia (50). Potential causes of failure of islet transplants

include failure of initial engraftment, inflammatory response at the transplant site, allo- or autoimmune response, and immunosuppressive drug-induced  $\beta$ -cell toxicity. The 1990–1995 data from the International Islet Transplant Registry (44) indicate that 6% of type 1 diabetic recipients achieve exogenous insulin independence at  $\geq 1$  year, although a greater percentage appear to have endogenous C-peptide production.

In contrast to the disappointing record of transplantation of islet allografts, islet autograft transplantation has been successful in nondiabetic patients with chronic painful pancreatitis (51–53). In these patients, abdominal pain was treated by total pancreatectomy, and islets were crudely separated from the pancreas in a few hours and then infused into the portal vein. Insulin responses to oral and intravenous glucose, as well as to intravenous arginine, are intact up to 7 years (52) and longer after autoislet transplantation. In one series, 74% of 14 patients receiving >300,000 islets were insulin-independent 2 years later (53). Thus, the number of allograft islets conventionally used for transplantation in diabetic patients (>500,000) should be sufficient to maintain insulin independence, if all things were equal. However, important differences between autografts and allografts are that the immunosuppressive drugs given to the allografted patients are known to adversely affect islet function, and autograft recipients have not previously undergone an autoimmune attack that resulted in diabetes. Development of more effective and less toxic immunosuppressive drugs may significantly improve the success rate of islet transplantation.

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