Pancreas Transplantation for Patients With Diabetes Mellitus

AMERICAN DIABETES ASSOCIATION

This document reviews the safety, efficacy, and indications for pancreas and islet transplantations as replacement therapy for patients with diabetes mellitus who require exogenous insulin.

CURRENT STATUS OF PANCREAS TRANSPLANTATION — By the end of 1990, ~3100 pancreas transplants are known to have been performed (1). In 1990, ~550 were performed in the U.S. (1); a similar number were performed in 1991. Thus, pancreas transplantation has changed from an occasional procedure to a frequently used therapy for selected patients.

The major clinical questions surrounding pancreas transplantation are *1*) its ability to achieve a permanent insulin-independent normoglycemic state; 2) its ability to prevent, retard, arrest, or reverse the chronic complications; and 3) its safety, with regard to the procedure per se and the requirement for prolonged immunosuppression.

Transplantation efficacy

The outcome of pancreas transplantation can be measured in several ways: *1*) patient life expectancy, 2) graft functional survival (i.e., insulin independence), 3) normalcy of the patient's metabolic state, 4) impact on diabetic complications, and 5) patients' quality of life.

Life expectancy. It is too early in the history of pancreas transplantation to estimate its ultimate impact on life expectancy, and little relevant data exist. One retrospective study of 232 patients with abnormal autonomic function or abnormal nerve conduction found that those with a functional pancreas transplant had better survival rates than patients with a failed transplant or no transplant (2). The critical question relative to life expectancy, i.e., the effect, if any, of transplantation on the development and progression of vascular disease, remains unanswered.

Graft functional survival. Pancreas graft survival rates are a function of several factors, including the surgical approach and whether the pancreas is transplanted along with a kidney. Data for 1021 cases in the United Network for Organ Sharing registry from October 1987 to October 1990 show 1-yr graft survival rates of 77% for simultaneous kidney-pancreas transplants, 52% for pancreas transplants subsequent to a kidney transplant, and 54% for pancreas-only transplants (1). The better functional survival rate of the pancreas graft in combined transplants is presumed due to the comparative ease with which kidney rejection episodes can be detected. The resultant changes in immunosuppressive therapy probably also protect the pancreas graft as well (3). Thus, more sensitive markers of early pancreas rejection are needed. Three-year graft survival rates of ~50% were reported by one major transplant center (4). The latter data were based on 181 transplant procedures performed from 1987 to 1990 and included both sequential and simultaneous pancreas-kidney transplants.

Improvements in rejection markers, HLA matching, surgical techniques, and immunosuppressive therapy are expected to continue to increase graft survival rates.

Metabolism. Several metabolic indexes can be used to measure transplant effects. Successful pancreas transplantation has been shown to eliminate the need for exogenous insulin and to result in normal or much improved glucose metabolism as measured by glucose tolerance tests and glycosylated hemoglobin determinations (4–12). However, in pancreas transplant recipients, insulin and glucagon responses to a glucose challenge, and certain other biochemical indexes may differ from those of nondiabetic patients. The long-term clinical significance of these disturbances is unclear.

It should be noted that a pancreas transplant closely approximates, but does not duplicate, the function of a normal pancreas. For example, in most cases, venous drainage of the transplant is into the systemic rather than the portal venous system (13). Thus, secreted insulin initially bypasses the liver and produces an elevated peripheral-portal venous insulin ratio, the ultimate significance of which remains to be determined. In addition, drugs used in immunosuppression regimens (e.g., glucocorticoids) may independently affect metabolism (14).

Quality of life. Daily insulin injections, self-blood glucose monitoring by fingerstick, hypoglycemic episodes, and dietary and other life-style restrictions characterize life with diabetes. Successful pancreas transplantations normalize or substantially improve glucose metabolism, eliminate the need for insulin injections and frequent glucose monitoring, and enable the patient to resume a more

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normal life-style. Several studies have detailed significant improvements in recipients' quality of life (12,15–18). However, in patients with solitary pancreas transplants, these benefits may be offset by the side effects of immunosuppressive therapy.

In a few patients with very poorly controlled diabetes not resulting from psychogenic factors, the day-to-day metabolic problems of diabetes are severe enough to be incapacitating (19,20). These patients tend to have recurrent episodes of ketoacidosis, often requiring hospitalization, or multiple episodes of severe hypoglycemic unawareness, which can be documented under controlled conditions (21–23). Medical treatment may be less than satisfactory in such patients. Pancreas transplantation has been reported to improve glucose counterregulation (24) and may be considered to improve the patients' quality of life and enhance their safety. As noted below, however, development of chronic diabetic complications, although common, is not inevitable in such patients and the effect of pancreas transplantation on these complications is unclear.

Effect on chronic complications. Though successful pancreas transplantation can produce significant and almost immediate improvements in patients' quality of life, of greater potential importance is their possible beneficial effect on the development and severity of the micro- and macrovascular complications of diabetes. However, for several reasons, only preliminary and incomplete data exist with regard to the effect of pancreas transplantation on these complications. Primary prevention studies require many years to determine clinically significant outcomes. Secondary intervention studies are hampered by the difficulty in assessing the window of reversibility for each complication. Currently, there are no reports of long-term prospective randomized controlled studies of the effect of pancreas transplantation on the complications of diabetes. Hence, prevention or attenuation of long-term complications is not a reason for considering transplantation at this time. Additional research on the effects of pancreas transplantation on chronic complications and life expectancy is encouraged.

One reason for adding a pancreas transplant to an already scheduled kidney transplant is the assumption that the patient's abnormal metabolic state eventually will damage the new kidney. A 1985 study examined diabetic patients who had received kidney-only (6 patients) or combined kidney-pancreas transplants (2 patients), and found that 2- to 3-yr posttransplant kidney lesions had developed in five of six kidney-only patients but not in the combined kidney-pancreas patients (25). However, another study in 18 patients 6- to 14-yr posttransplant demonstrated that not all diabetic patients with kidney-only transplants develop the histological lesions of diabetic kidney disease. Thus, the long-term incidence of diabetic nephropathy in transplanted kidneys is unknown, and undefined factors intrinsic to the kidney itself may operate to modulate diabetic renal disease (26). A study of 12 subjects who received pancreas transplants after having undergone renal transplantation found that they had significantly less severe histological changes in the glomerulus than a control group of diabetic renal transplant patients treated with conventional insulin therapy (27). These data support the hypothesis that normoglycemia achieved through pancreas transplantation may prevent or retard the progression of diabetic renal disease.

The possibility that pancreas transplantation can arrest and, to a limited extent, reverse the progression of diabetic polyneuropathy has been suggested by some studies. One study compared the neurological status of 61 neuropathic patients with insulin-dependent diabetes who were given a pancreas transplant with a control group of 48 patients with similar neurological characteristics who were treated only with a nonintensive insulin regimen (28). Neuropathy tended to worsen during the 42-mo study in the control group but improved in the patients who received transplants. (The study design did not provide for comparison of transplantation vs. intensive insulin therapy and was not randomized.) Two smaller, shorter studies reported some neurological stability or improvement posttransplant (29), but this may have been due to the elimination of uremia rather than the metabolic effects of the pancreas transplant (30).

Pancreas transplantation does not appear to affect preexisting moderate to severe retinopathy (31), although it has been suggested that transplantation early in the course of the retinopathy might be beneficial (32).

Transplantation safety

In the 25 yr since the first pancreas transplant, 1-yr patient survival rates have risen continuously from 41% in 1966–1977 to 92% in the 1987–1990 interval (33). Three-year patient survival rates from three transplantation programs were reported to be 85–90% (4,12,34). The most recent survival rates are similar to those of kidney-only transplants in the general population (36). Over 90% of pancreas transplants have been conducted simultaneously or after a kidney transplant in patients who, therefore, already were obligated to immunosuppressive therapy. Kidney transplantation is the preferred therapy for uremia in diabetic patients. With current patient selection procedures, 1-yr survival of combined pancreas-kidney transplant recipients is similar to that of kidney-only transplants (1,35). For pancreas-only transplants, the 1-yr patient survival rate in 72 cases was 92% (1).

The mortality risk of pancreas transplantation procedures either alone or combined with kidney transplants, is similar to that of kidney transplantation, i.e., small, but not negligible. In combined kidney-pancreas transplants, the risk is small enough so that such surgery can be considered as an alternative to dialysis and continued insulin therapy in many uremic diabetic patients. However,

uremic recipients of kidney-pancreas transplants have a higher renal rejection episode rate and longer hospitalization than recipients of kidney-only transplants (36).

Surgical complications of pancreas transplantation include bleeding, local infection, urinary leak, graft pancreatitis, bicarbonate loss, and urethritis (34). Postoperative aggravation of existing gastrointestinal motility problems may occur. Average postoperative hospital stays of 18 days for 33 simultaneous kidney-pancreas transplants and 10 days for a similar group of 18 kidney-only transplant patients were reported by one institution (4). The dual transplant patients also had a significantly higher readmission rate for complications than the kidney-only patients. Attention to surgical technique and appropriate antibacterial prophylaxis are essential to minimize complications.

The risk-benefit ratio for pancreas-only transplants in nonuremic patients is more difficult to assess. The primary long-term risk of pancreas transplantation (other than graft failure) is the toxicity of the drug therapy necessary to prevent both rejection of the organ and autoimmune destruction of the transplanted β-cells. This therapy consists of combinations of immunosuppressive agents (e.g., cyclosporine, azathioprine, and prednisone), and in some situations, other agents such as antilymphocyte globulin. These drugs have numerous and varied significant adverse effects including nephrotoxicity, infection, hypertension, and gingival hyperplasia. Recipients of kidney allografts require lifelong immunosuppression, the risk of which, although significant, generally is outweighed by the poor quality of life and mortality of end-stage renal disease. Combining a pancreas transplant with a kidney transplant imposes little additional risk of drug toxicity beyond that which already exists from the immunosuppression needed by the renal graft. This is not true for pancreas-only transplants; such patients incur a substantial exposure to drug-induced nephropathy and other adverse effects from immunosuppression that they otherwise would not experience.

Several new immunosuppressive agents (e.g., FK-506) thought to be less toxic than those currently available are in clinical trials. If these drugs prove to be significantly safer than those now used, the risk-benefit ratio of pancreas-only transplants will need to be reassessed.

Other risk factors should be considered in patient selection for pancreas transplantation with or without a kidney. For example, patients with surgically uncorrectable vascular disease frequently are poor candidates for transplantation procedures.

Transplant costs

All organ transplants are expensive and cost is an increasingly important consideration in establishing the appropriateness of medical care procedures. Only limited, incomplete data exist on the cost of pancreas transplantation. One report indicated that the average hospital charge for pancreas-only transplants in 1988 was $70,000 (37). This figure did not include physician fees or organ acquisition costs and represented billed charges, not actual amounts paid. Another study reported the median cost in 1988 to be $67,000, including hospital charges, physicians' fees, and donor organ acquisition costs (38). This cost reflected a median hospital stay of 21 days.

Islet cell transplantation

Islet cell transplantation offers potential advantages over pancreas transplantation. It is a minor rather than major surgical procedure and may thereby offer the possibility of being safer than a pancreas transplantation. Islet cells potentially can be altered in vitro or isolated in devices so as to obviate the need for posttransplant immunosuppression. Furthermore, if animal islet cell transplantation proves successful, the supply of islet cells is potentially much greater than that of whole human glands. Islet transplantation has been performed in only a small number of patients, and a few have achieved transitory insulin independence (39,40), and in one, insulin independence has persisted for >1 yr (41). However, the probability of achieving prolonged insulin independence with an islet transplant remains very low at this time. Many questions regarding islet transplant sites and methods, islet cell processing, and immune rejection must be addressed successfully before islet cell transplantation can be characterized as more than an investigational procedure. The American Diabetes Association encourages research into this promising procedure.

RECOMMENDATIONS

1. Pancreas transplantation should be considered an acceptable therapeutic alternative to continued insulin therapy in insulin-dependent patients with end-stage renal disease. These patients should also *1*) meet the medical indications and criteria for kidney transplantation, 2) have significant clinical problems with exogenous insulin therapy, and 3) not have excessive surgical risk for the dual transplant procedure. The pancreas transplant can be performed either simultaneously or after the kidney transplant. Third-party reimbursers of medical care should include coverage for pancreas transplantations that meet these criteria.

2. The current data on the long-term effects of transplantation on life expectancy and diabetic complications are insufficient and, per se, do not justify pancreas transplantation.

3. Pancreas transplantation in the absence of renal failure is not recommended except in those few, unusual patients who exhibit *1*) a history of frequent acute severe metabolic complications that require medical attention, 2) have

clinical and emotional problems with exogenous insulin therapy that are so severe as to be incapacitating, and 3) consistent failure of other therapeutic approaches to ameliorate the situation. Institutional guidelines for assuring an objective, multidisciplinary evaluation of the patient's condition and eligibility for transplantation should be established and followed. Third-party payor coverage is appropriate only where such guidelines exist.

4. Islet cell transplantation is a clinical investigational procedure.

5. Institutions that perform islet or pancreas transplantations should be tertiary care centers that have an active kidney transplant program and are equipped to adequately handle the complex medical and psychosocial needs of transplantation patients.

6. An adequate supply of human pancreatic tissue is essential for continued transplantation progress; therefore, the American Diabetes Association urges increased efforts to expand the supply of pancreatic tissue for clinical and research purposes.

APPENDIX— This technical review was written by a committee chaired by Daniel Porte Jr, MD, University of Washington and Veterans Administration Medical Center, Seattle, WA. Members of the committee were Lester Baker, MD, Children's Hospital, Philadelphia, PA; R. Randall Bollinger, MD, PhD, Duke University Medical Center, Durham, NC; Saul Genuth, MD, Mt. Sinai Medical Center, Cleveland, OH; David W. Scharp, MD, PhD, Washington University, St. Louis, MO; and David E.R. Sutherland, MD, PhD, University of Minnesota, Minneapolis, MN.

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