REVIEW

CME CREDIT

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Pancreas transplantation in type 1 diabetes: Hope vs reality

ABSTRACT

Pancreas transplantation can improve quality of life for patients with type 1 diabetes by eliminating hypoglycemic and hyperglycemic episodes, the need for insulin injections, frequent self-monitoring of blood glucose levels, and dietary restrictions. Increasing evidence suggests that it may slow the progression of long-term diabetic complications. On the other hand, patients risk the adverse effects of lifelong immunosuppression.

KEY POINTS

Pancreas transplantation is an alternative to insulin therapy in type 1 diabetic patients with end-stage renal disease who plan to undergo kidney transplantation. Simultaneous kidney and pancreas transplant offers excellent outcomes.

Patients may be placed on the cadaveric-organ list *before* dialysis is needed, making early referral a crucial part of the patient's overall management.

When possible, a kidney from a well-matched related donor offers the best long-term results for dialysis independence. A recipient of a related-donor kidney (or a previously placed cadaver donor kidney) may be a good candidate for later pancreas transplantation.

Patients without end-stage renal disease may be eligible for a pancreas transplant if they have severe, recurring metabolic complications.

BECAUSE OF EXTENSIVE PUBLICITY about the promise of pancreas and islet cell transplantation, many patients with type 1 diabetes are asking their primary care physician about these procedures, in the hope of freeing themselves from dependence on exogenous insulin.

Are the hopes justified? To help physicians answer these questions, in this article we evaluate current recommendations for pancreas and kidney transplantation, including preemptive transplantation, for preventing and treating the major complications of type 1 diabetes mellitus. We also discuss the current state of research into human and porcine islet cell transplantation.

BACKGROUND

Approximately 16 million people in the United States have diabetes mellitus. Until the discovery of insulin by Banting and Best in 1921, the disease was generally fatal. Even today, every year up to 180,000 Americans die of complications of diabetes, and many more suffer diabetes-related blindness, renal failure, peripheral and autonomic neuropathies, or vascular occlusive disease.[1]

The landmark Diabetes Control and Complications Trial (DCCT)[2] conclusively demonstrated that tight glycemic control can reduce the risk for retinopathy, nephropathy, and neuropathy in patients with type 1 diabetes. However, tight glycemic control was difficult to achieve and also increased the risk of hypoglycemia.

Against this background, the prospect of curing diabetes through pancreas transplantation has great appeal, and indeed, efforts were

already underway at the time of the DCCT study.

TECHNICAL HURDLES OVERCOME

Early work with pancreas transplantation encountered two major hurdles: preserving the pancreas between procurement and transplantation, and finding a way to drain the exocrine secretions of the pancreas in the recipient.

In the mid-1980s, Belzer and Southard[3] solved the first problem by developing a cold-storage solution that markedly decreased the incidence of early pancreatitis and thrombosis to the current rates of 3% to 4%. This solution allows for preservation of the pancreas up to 24 hours.

Around the same time, surgeons developed several procedures to solve the problem of exocrine drainage. Currently, the preferred procedure is to harvest the pancreas, sphincter of Oddi, and a loop of duodenum as an intact unit, and then graft this duodenal loop onto the recipient's bladder, creating an anastomosis, as initiated by Ngheim and others (FIGURE 1).[4–6]

Early benefits: no insulin injections and fewer dietary restrictions

However, this procedure has drawbacks. Early urologic complications include hematuria and urinary infections. In some men, urethritis can develop, rarely with strictures or urethral disruption. (Urinary complications are easily managed in a majority of patients, with 10% to 20% requiring surgical revision of the anastomosis.) Another drawback is that patients lose fluid and bicarbonate in the urine and usually need oral supplementation of fluid and minerals.

In light of these drawbacks, another method is gaining popularity: enteric drainage via anastomosis of the loop of donor duodenum directly into the intestine (FIGURE 1).[7] In addition, some groups use the superior mesenteric vein for venous drainage and the duodenum for exocrine drainage (FIGURE 1).

BENEFITS AND RISKS OF PANCREAS TRANSPLANTATION

Some of the benefits of pancreas transplantation are immediate: no more fingersticks and glucometric measurements (or fewer of them), no more insulin injections (or lower doses of insulin), and more flexibility in diet. Not surprisingly, in a study,[8] patients with combined pancreas-kidney transplants reported they had a better quality of life than did age-matched controls with kidney transplants only.

This observation raises the question of how to define "success" in pancreas transplantation. Most investigators define it as *complete* insulin-independence.[5,6] However, even if the graft has only partial function, the patient may consider the operation a success if he or she can avoid marked hypoglycemia or hyperglycemia and take lower insulin doses.

The long-term benefits of pancreas transplantation are extrapolated from the DCCT data and lead us to believe that if one can improve glycemic control to the point where the glycohemoglobin level is normal, one might reduce the risk of long-term diabetic complications. Furthermore, preliminary findings are promising, including the following[9–13]:

Visual acuity can improve when glucose levels are consistently normal. This effect is thought to be a result of fewer glycosylated proteins in the eye chamber and decreased osmotic shifts with fluctuating glucose levels. (However, no distinct beneficial effect on retinopathy has been demonstrated.)

Improved gastric emptying has been documented using nuclear scans and electrogastrography.

Nerve conduction velocities increase even when controlled for the nonuremic state, though often the patient may not sense the millisecond improvements.

Early diabetic nephropathy was shown to reverse in elegant electron micrographic studies in patients who received a pancreas after a kidney.

Skin oxygen tension has been shown to increase after pancreas transplantation.

Immunosuppression poses risks

Nevertheless, transplant recipients must take immunosuppressive drugs as long as the transplant is functioning, and these drugs increase the risk of infection and cancer. In addition, some immunosuppresive drugs are nephrotoxic, cause hypertension, and can have troubling cosmetic effects such as acne, hypertrichosis, and gingival hyperplasia. Newer immunosuppressive regimens allow some patients to take

lower doses of corticosteroids. Still, any immunosuppressive drug can have significant side effects.

MOST PANCREAS RECIPIENTS ALSO RECEIVE A KIDNEY

Of the nearly 1,800 pancreas transplants performed worldwide every year (1,100 of them in the United States), nearly all are in type 1 diabetic patients who are also receiving a kidney transplant because of end-stage renal disease. The percentages break down as follows[14]:

- Simultaneous pancreas and kidney transplantation (often abbreviated as SPK)—90%
- Pancreas transplantation after kidney transplantation (PAK)—9%
- Pancreas transplantation alone (PTA)—1%.

KIDNEY TRANSPLANTATION IN DIABETIC PATIENTS

Diabetic nephropathy (albuminuria > 500 mg/24 hours) carries a poor prognosis. Without treatment, renal function progressively deteriorates. Aggressive management of blood pressure with angiotensin-converting enzyme inhibitors can slow the rate of decline of renal function by approximately half.[15] However, most patients eventually require dialysis or transplantation. Moreover, those who enter dialysis tend not to do well: more than 50% of type 1 diabetic patients who begin dialysis die within 5 years.[16]

For these reasons, clinicians should consider kidney transplantation—and possibly simultaneous pancreas and kidney transplantation—for diabetic patients with nephropathy, since survival rates are higher in those who receive a kidney transplant (FIGURE 2).[16] By talking about transplantation early on, one can explore the options of related-donor kidney transplantation or evaluation and placement on a waiting list for cadaveric kidney or kidney-pancreas transplantation.

Related donor vs cadaveric donor

Transplantation of a kidney from a related donor confers the most favorable outcomes, particularly when the donor's HLA profile is well matched or identical to the recipient's.

Options for pancreas transplantation

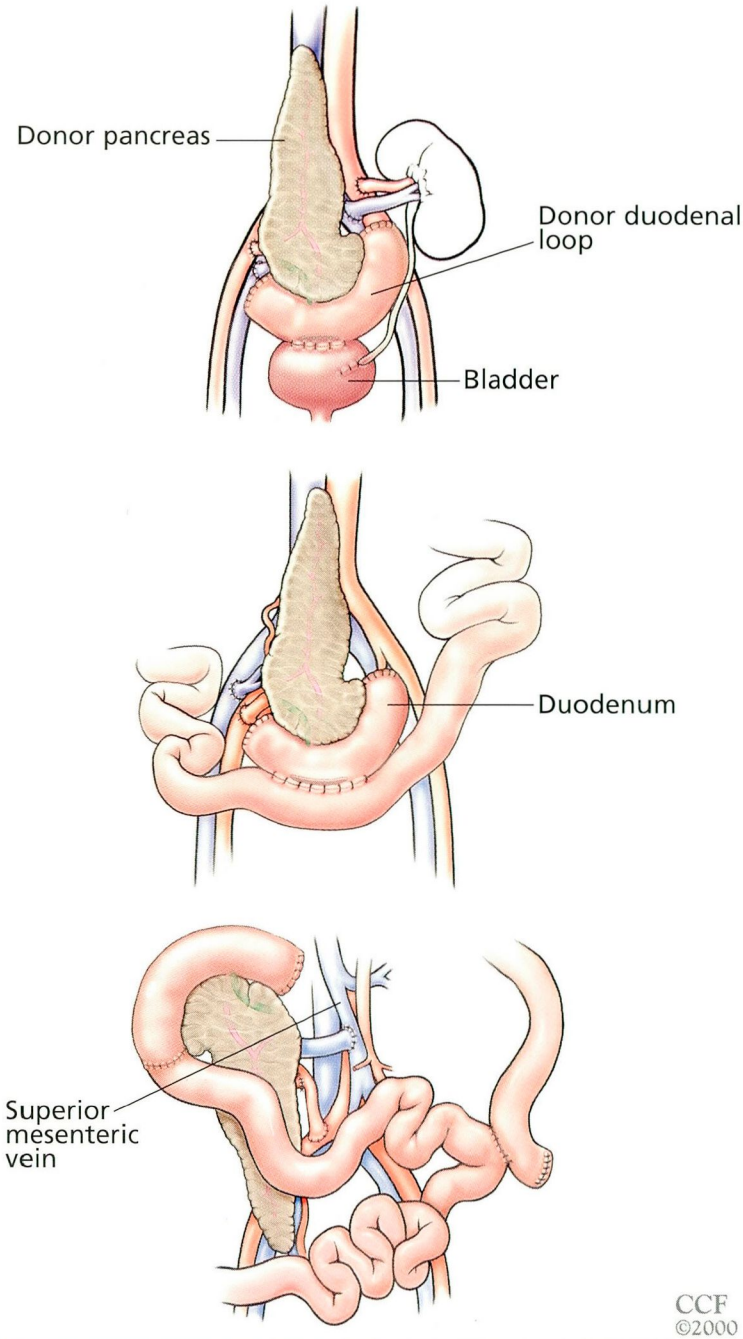

FIGURE 1. Three surgical options for pancreas transplantation. **Top,** procedure developed by Ngheim and others, in which the exocrine secretions of the pancreas are drained into the bladder. **Middle,** enteric drainage into the duodenum. **Bottom,** enteric drainage into the duodenum and venous drainage into the superior mesenteric vein.

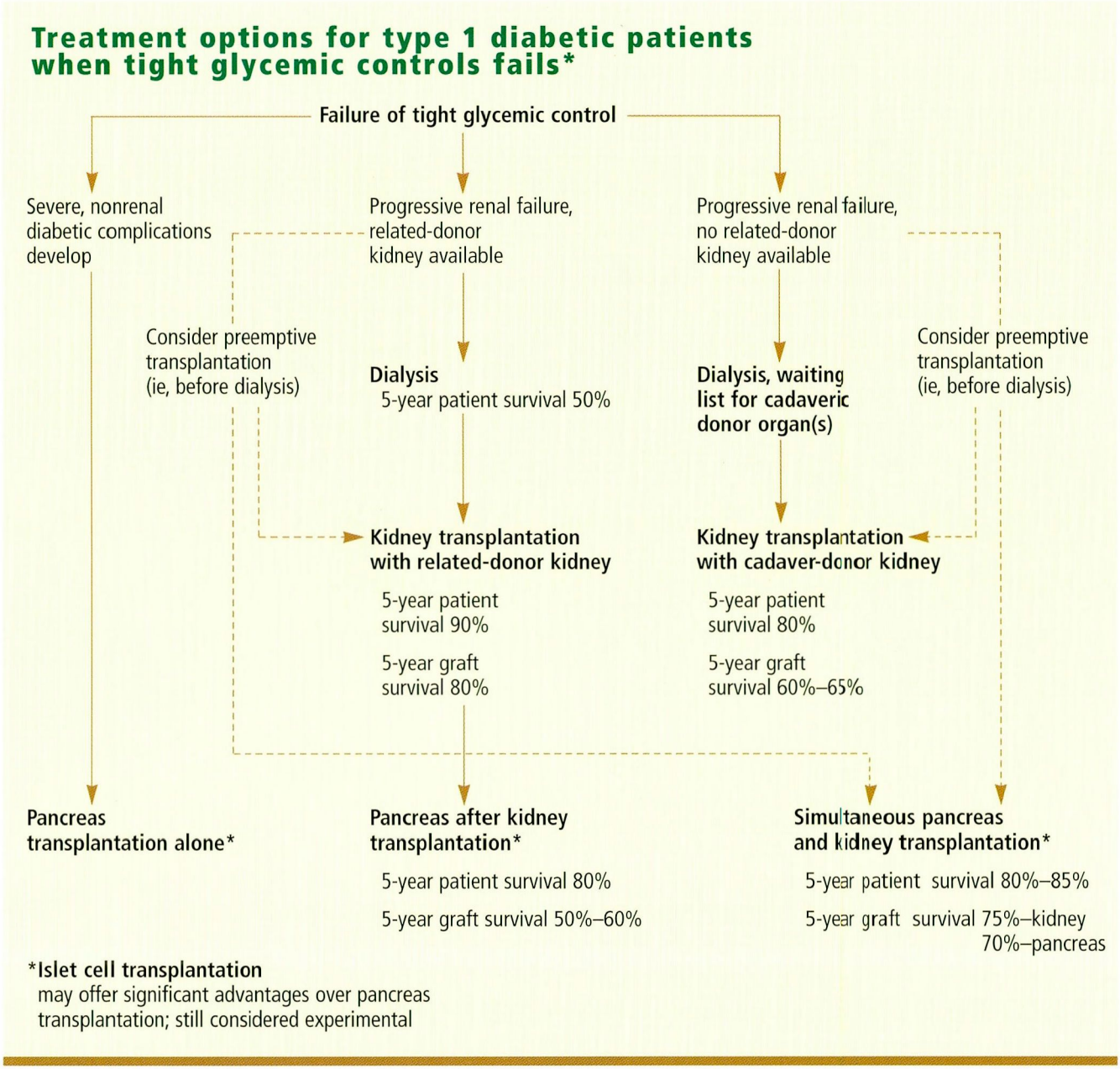

FIGURE 2

Overall, the chance of graft survival of more than 5 years approaches 80%.[17] Moreover, with a related-donor kidney, the recipient avoids an extended period on dialysis and a potentially long wait for a cadaveric kidney. A pancreas transplant could be considered at a later date.

Preemptive transplantation

On occasion, preemptive (before dialysis) kidney transplantation or kidney-pancreas transplantation is possible, and probably preferable. In patients well enough to undergo simultaneous pancreas and kidney transplantation, the median time on a waiting list for a cadaveric organ is similar to that for a first cadaveric kidney. Current policies for placing a patient on the waiting list for a cadaveric organ specify that the patient's glomerular filtration rate be less than 20 mL/minute. Thus, patients may be evaluated and placed on the list *before* dialysis is needed,

making early referral a crucial part of the patient's overall management.

SIMULTANEOUS PANCREAS AND KIDNEY TRANSPLANTATION

Patients whose diabetes is difficult to control and who may soon need dialysis (ie, with a glomerular filtration rate < 20 ml/minute) or are currently on dialysis may benefit from simultaneous pancreas and kidney (SPK) transplantation.

Fortunately, because kidneys used in the simultaneous grafting procedure have ischemia times similar to those of related-donor kidneys and are often from younger donors, the 5-year survival rates approach or even exceed rates obtained with related-donor kidney transplantation.[18]

On the other hand, simultaneous pancreas-kidney transplantation involves two transplants and thus carries twice the risk of a kidney transplant in age-matched and disease-matched analyses of morbidity.[19]

Patients with diabetes are well known to be at high risk of occult vascular disease. Preoperative risk assessment should include carotid and peripheral arterial vascular studies, cardiac stress testing, and coronary angiography, when appropriate. The additional risks may not be justified in some patients with irreversible diabetic disease in other organ systems.

PANCREAS TRANSPLANTATION AFTER KIDNEY TRANSPLANTATION

Another option is pancreas-after-kidney (PAK) transplantation—preferably, related-donor kidney transplantation, followed at a later date by pancreas transplantation. This option is becoming more popular because it permits patients to stop dialysis sooner, while still being considered for pancreas transplantation.

This approach has been historically less successful than simultaneous pancreas-kidney transplantation: the 5-year survival rate for the pancreas graft is 30% to 40%. However, with newer immunosuppressive drugs and better tissue matching, some centers are now achieving 5-year graft survival rates of 50% to 60%. Still, this approach requires two operations and, in at least one cost analysis, is more expensive.[20]

Of note: If pancreas transplantation is contemplated for the future, the surgeon should try to place the donor kidney on the left side. This will allow the pancreas to be placed on the right side, which carries markedly fewer technical complications than left-sided pancreas transplantation.[21]

PANCREAS TRANSPLANTATION ALONE

In patients who have life-threatening complications of diabetes (eg, severe episodes of hypoglycemia) but do not yet have severe renal disease, pancreas transplantation alone may be considered if the benefits outweigh the risks of immunosuppression. This operation can now be performed with acceptable success rates (40%–50% 4-year survival free of insulin). However, the effects on long-term diabetic complications such as retinopathy and diabetic neuropathy are not yet known. In addition, it is difficult to predict which patients are at greatest risk of end-organ damage and, therefore, are in greatest need of pancreas transplantation.[22]

Consider transplantation before renal failure occurs

ISLET CELL TRANSPLANTATION: COMING CLOSER TO SUCCESS

Why transplant the whole pancreas, when only the islet cells are needed? Islet cell transplantation, performed by infusing a suspension of islet cells percutaneously, would avoid the complications of open surgery. This procedure is still experimental but is closer to becoming a meaningful therapeutic option.[22]

A few patients have achieved insulin dependence after receiving allogeneic intraportal islets with a liver transplant.[23,24] Furthermore, newer immunosuppressive regimens may decrease the islet rejection rate, which is currently thought to be the major reason for lack of long-term success with islet cell transplantation.

Another problem is how to procure enough islet cells—approximately 500,000 per patient. For years, human islet cells were difficult or impossible to procure and purify, and several donors were needed to supply enough islet cells to treat a single patient.

Some centers now report reasonably consistent results with automated processes that purify enough islets from a single donor to treat a single patient. Autologous transplantation after pancreatectomy has been successfully achieved.

With the advent of stem cell isolation and cell engineering, it is hoped that in the future we will engineer and grow islet cells in plentiful supply,[25,26] and patients with diabetes might receive periodic infusions of cells that might last until immune or autoimmune destruction occurs. Perhaps by that time the etiology of diabetes might be uncovered and prevention of diabetes might be feasible. At present, however, given the limited donor supply and the current success rates with whole-organ transplantation, consistent success needs to be achieved before islet cell transplantation can be widely used.

Half of diabetic patients on dialysis die within 5 years

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